The evaluation of a novel imaging-based complex diagnostic and therapeutic pathway intervention for men who fail radiotherapy for prostate cancer

Ana Abhiramy Kanthabalan
MBChB BA MRCS
UCL
PhD Thesis
Division of Surgery and Interventional Science
Date of Submission 18/03/2018

I, Ana Kanthabalan confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Acknowledgement

I would like to thank Professor Mark Emberton and Professor Hashim Ahmed for appointing me as a Clinical Research Fellow at UCLH. Their vision to change the face of prostate cancer diagnostics and treatment has been inspiring. They have been hugely supportive throughout my time as a research fellow. I am greatly thankful for all their support that has allowed me to publish and present internationally and now fulfil my dream of becoming a Urologist.

I want to thank Caroline Moore and Manit Arya for giving me feedback and support on my publications and conference presentations. I wish to thank Neil McCartaan for his support as data manager. His apt skills at creating database registries and coding will forever help me. I wish to thank him and Malisha Maru for their help in data collection which has helped in my publications.

I wish to thank Shonit Punwani and Navin Ramachandran for showing me how to interpret pelvic MRIs and for reviewing my papers. I wish to thank them for the help in the setup of clinical trials and for MRI reporting in these trials. I wish to thank Athar Haroon for his help in the setup of the FORECAST trial and for interpreting and reporting the nuclear medicine scans for this trial. I am indebted to Max Peters who has helped me in the statistical analysis of my papers. He has been a great support in the writing of my thesis.

Lastly, I wish to thank my parents for all their love, help and support through medical school and keeping me calm when I needed it the most. As my father always says, ‘when one door closes another opens’…an opportunity is always out there. I am so grateful for this one.

Abstract

Background: One-third of men may experience biochemical failure by 8 years following radical radiotherapy for prostate cancer. Focal salvage therapy (FST) may offer further curative treatment. Before FST, distant disease must be ruled-out and intra-prostatic disease must be accurately detected and characterised.

Aim: The aim of this thesis was to evaluate novel diagnostic and staging techniques and outcomes of focal salvage treatments for radiorecurrent prostate cancer.

Methods: Both retrospective and prospective data will be presented. A retrospective analysis was conducted to compare a) Bone scan with Choline PET/CT in the detection of distant metastases b) Accuracy of MRI-Targeted Biopsy (MRI-TB) with whole-gland template mapping biopsy (TPM) c) the outcomes of focal salvage HIFU (FS-HIFU). These retrospective analyses provided important inputs into the design and conduct of the prospective trial FORECAST - Focal RECurrent Assessment and Salvage Treatment. Key trial outcomes were a) detection rate of distant metastatic disease of Whole Body MRI compared to other staging scans b) detection rate of MRI for clinically significant prostate cancer and c) Short-term outcomes of focal salvage therapies.

Outcomes: Within the retrospective analyses, there was poor concordance with bone scan and Choline PET/CT in the detection of metastatic disease (kappa value 0.024). MRI-TB had lower detection rates of clinically significant cancer compared with TPM biopsy; 77.9% vs. 85.7% (p=0.146). The b-DFS rate post FS-HIFU was 48% (95% CI 39–59) and composite end free survival was 40% (95% CI 31–50). In the prospective analyses, there was moderate agreement between WB-MRI and Choline PET/CT for bony metastatic disease (Kappa=0.411 (p<0.0001)). MRI (PIRADS 4) had a high sensitivity, specificity, PPV and NPV for the detection of clinically significant cancer 90%,

81.3%, 85.7% and 86.7%. b-DFS rates post FS-HIFU and FS-cryotherapy was 73% (95% CI 51-100) and 67% (95% CI 30-100) at 12 months (p=0.95).

Impact Statement

In 2015 in the UK approximately 47,151 men were diagnosed with prostate cancer. Up to 30% of these men went on to have radiotherapy and up to half of these men will have biochemical relapse (rise in PSA) within ten years of primary radiation treatment. For these 7000 men who are suspected to have radiorecurrent disease, hormones are the main form of treatment offered. Hormones however only control disease (for up to three years) and do not provide a cure; this can have significant impact on patients' well being.

Further localised prostate treatments (salvage therapy) may be an option for these men, but it is important to accurately characterise radiorecurrent disease. It is felt that men who fail radiotherapy and are found to have widespread metastatic disease, will not benefit from further localised prostate treatment. Thus, it is important to diagnose intra and extra prostatic disease accurately.

The aims of this thesis were to find better techniques at diagnosing metastatic and localised radiorecurrent prostate cancer and reducing morbidity of salvage treatment by providing focal salvage treatment, where only the area of radiorecurrent disease was targeted and treated. Several potential benefits were found.

Firstly, there could be a further drive to advance diagnostic scans for radiorecurrent prostate cancer. Currently patients suspected of having recurrence post radiotherapy must undergo two staging scans – Choline PET/CT and bone scan – both involving exposure to radiation and having poor accuracy at low PSA levels (PSA <20 ng/ml). This means that recurrence may not be identified until the cancer has metastasized which then limits patients to systemic hormonal treatment. It is therefore imperative that new imaging is capable of scanning the whole body and able to identify any recurrence at low levels of PSA. Our prospective study compared Whole Body-MRI to Choline PET and Bone scan and found a moderate agreement between WB-MRI and Choline PET/CT (Kappa score 0.548 (p=0.00032)) in

the detection of NX-0 nodal disease and for bony metastatic disease (Kappa=0.411 ($p<0.0001$)) which was significant. There was fair agreement for bony metastatic disease detected by WB-MRI and BS (kappa score 0.333 $p=0.157$) and also for Choline PET/CT and BS (Kappa = 0.333 ($p=0.46$)) however significance was not achieved.

Secondly there may be further development in the minimally invasive and focal treatments for radio-recurrent disease. Issues following radiotherapy are often that there is significant fibrosis and scarring which can lead to significant side effects such as recto-urethral fistula. Developing or refining current treatment that targets recurrent cancer within the prostate, allowing for these structural changes and minimising further damage is also important. Our retrospective study examined FS-HIFU with tolerable side effect outcomes; UTI in 11.3% of patients, epididymitis in 1.3%, bladder neck strictures in 8%, rectourethral fistula after first HIFU in 2%and osteitis pubis in 0.7%.
Our prospective study has shown the potential of focal salvage HIFU and cryotherapy as a salvage treatment post radiotherapy. b-DFS rates post FS-HIFU was 93% (95% CI 80-100) at 6 months, and 73% (95% CI 51-100) at 12 months ($p=0.95$). For focal salvage cryotherapy this was 100% and 67% (95% CI 30-100) respectively ($p=0.95$). Only one patient developed Clavien 3b complication – urethral stricture requiring dilation - and there are no prostate cancer related deaths at present.

Thirdly, follow up of these patients for minimum of ten years is necessary. This means that prospective databases should be kept up to date. This allows future researchers, to formulate algorithms determining the outcomes of each treatment. A new risk classification can be created which could be based upon baseline risk prior to radiotherapy, re-staging information and treatment outcomes, to determine those who may benefit from salvage treatment or systemic therapy. The research conducted within this study is the first to produce a composite failure rate after salvage therapy. This consisted of a patient failing by any of the following parameters; BCF and/or positive localized or distant imaging and/or positive biopsy and/or systemic therapy and/or metastases and/or prostate cancer-specific death. Within this research,

following focal salvage HIFU, univariable analyses showed that primary Gleason score 8–10, T stage 3 before salvage HIFU, and PSA-nadir post-salvage achieved statistical significance for the composite endpoint. A risk model can therefore be calculated as a point scoring system, similar to D'Amico risk score, that takes into account primary and salvage baseline characteristics to determine those suitable for focal salvage therapy. The outcomes from the FORECAST study will aid in the prediction model.

Lastly the impact on public policy for patients post primary treatment (radiotherapy) in this instance could be changed dramatically. There will be a focus on a systematic flow of patients from time of biochemical failure to accurate re-staging and tailored treatment.

Having a single re-staging scan, in this case Whole-body MRI (PSMA Choline PET/CT which is gaining popularity in the diagnosis of metastatic prostate cancer was not initially available at time of trial set up and therefore could not be incorporated) as opposed to three scans is obviously less burden on the patient in terms of time spent at hospital but also exposure to radiation. Fewer scans and need for radioactive tracers could save costs. In the United Kingdom, sample costs for MRI may vary from up to £899 this is compared to CT (up to £665) and bone scan (£473) which have a total cost of up to £1138.

Following re-staging, patients would then be classified into risk – low, intermediate and high risk, according to PSA, site of recurrence, number of distant metastases and could incorporate age and other co-morbidities.
This is important as post radio-recurrence and re-diagnosis, patients may be significantly older than at the time of their initial radiotherapy. Risk of general anaesthetic and invasiveness of treatment therefore, must be considered.

The key is to then have a number of treatment options available– focused, whole gland or systemic – from which patients classified into a risk category at re-staging will have treatments most likely to benefit them.

Chapter 1 Table of Contents

Abbreviations

PSA - prostate-specific antigen

EBRT - external beam radiotherapy

ADT – Androgen Deprivation Therapy

MpMRI/MRI – Multiparametric magnetic resonance imaging

WB-MRI – Whole Body MRI

TPM - transperineal prostate mapping

MRI-TB – Magnetic Resonance Imaging Targeted Biopsy

TRUS – Transrectal Ultrasound

BS – Bone Scan

PSAdt -PSA doubling time

PSAvel - PSA Velocity

IQR - Interquartile range

OR - odds ratio

BF – Biochemical Failure

b-DFS – Biochemical Disease Free Survival

CEFS – Composite end free survival

UCLA-EPIC - Expanded Prostate Cancer Index Composite

FORECAST – FOCal RECurrent Assessment and Salvage Treatment

IPSS - International Prostate Symptom Score

IIEF - International Index of Erectile Function

Chapter 1 Introduction

In this chapter, the background of radiorecurrent prostate cancer, methods of re-staging, local (intra-prostatic) diagnosis and current salvage treatment options will be discussed.

1.1 Background of radiorecurrent prostate cancer

Prostate cancer is the most common cancer amongst men aged over 70 years (1,2). External beam radiotherapy (EBRT) is a common treatment for prostate cancer, however up to 50% of patients can develop biochemical recurrence within ten years of primary radiation treatment (3-8). Failure following EBRT is typically detected by rising PSA and is defined as a rise by 2 ng/ml or more above the nadir PSA post treatment – Phoenix definition (9).

The difficulty with PSA progression following primary therapy is whether this is due to recurrent local, regional or metastatic disease (10,11). It is widely reported however, that men who fail primary EBRT are commonly started on systemic adjuvant hormonal therapy (12,13). Indeed, one study found that 63% of patients treated with EBRT developed recurrent disease and 93% of these received Androgen Deprivation Therapy (ADT) as the salvage treatment (14). Significant side effects such as weight gain, breast enlargement and tenderness, hot flashes, lethargy, osteoporosis and fracture risk, increased cardiovascular comorbidity and metabolic syndrome (15-17). Hormones are expensive and once started can lead to castrate resistance within 2 years with subsequent costly therapies. Thus, it is important to determine the site of recurrent disease as this determines the suitability of further local or systemic treatment (18,19).

1.2 Current re-staging techniques

Currently bone scan and Choline PET/CT are used in the re-staging of individuals suspected to have prostate cancer recurrence following

radiotherapy.

1.2.1 Bone Scan

After primary treatment of prostate cancer, bone is the first site of relapse in more than 80% of cases (20). Plain film and bone scans (BS) form the mainstay of detection. BS can detect metastases up to 18 months before plain film. There only needs to be a 10% change in bone mineral turnover to be detected by BS, whereas the bone must demineralise by 50% before a lesion is detected by plain film (21). BS and plain film have been shown to underestimate the true incidence of metastatic disease. Bubendorf et al. (22) performed autopsies on 1,589 men with prostate cancer (47 % were unsuspected), and the incidence of metastatic bone disease was 90%. BS are also well known for its high rate of false positives resulting from degenerative change, inflammation, Paget's disease and trauma.

Detection rates of bone scan are dependent upon PSA level, clinical stage and Gleason score (1). In patients with PSA level 10-20ng/ml detection rates are at 33% vs. 38.5% in men with PSA level of 20-50 ng/ mL (1). A high tumour stage >T3 appears to have the highest rate of bone scan positivity, up to 90.7% (1). Due to the poor specificity of bone scan, further correlation is often required with X-Rays exposing patients to further radiation (23).

1.2.2 Choline PET/CT Scan

There are now several radiotracers able to visualise different tumour metabolisms are currently available, including 18F- fluorodeoxyglucose for glucose metabolism (18F-FDG), carbon 11(11C)/fluorine 18 (18F)-labelled choline (11C/18F Choline) and 11C-acetate for lipid metabolism, 11C-methionine for amino acid metabolism and deoxy-18F-fluorothymidine for imaging cell proliferation (24).

In tumour cells, there is an increased expression of cellular membrane glucose transporters and enhanced hexokinase II enzymatic activity in tumours resulting in a higher rate of glucose metabolism, which can be identified by 18F-FDG PET (11). However, 18F-FDG cannot distinguish between post-therapy changes and recurrent tumour cells or prostatitis. Also, high levels of 18F-FDG are excreted in the urinary bladder which can mask any lesions in the vicinity (11). 18F- or 11C-Acetate tracers are taken up by tumour cells within the prostate due to increased fatty acid synthesis (11,25). 11C-Acetate has the advantage of not accumulating within the bladder unlike 18F-FDG. 18F- or 11C-Choline radiotracers have been examined due to the upregulation of choline kinase in prostate cancer tumour, which leads to the incorporation and trapping of choline within the cell membrane. 11C-choline also has the advantage of minimal urinary excretion (11). Currently, of these radiotracers 18F-FDG is of limited value and whilst the other tracers hold promise there is still no recommended gold standard PET/CT tracer (1).

Among the different PET tracers evaluated for prostate cancer imaging, 11C/18F choline has been particularly investigated. Choline is an essential component of phospholipids of the cell membrane. Cell proliferation and upregulation of choline kinase are two mechanisms suggested for the increased uptake of this tracer in prostate cancer (26). The presence of choline transporters also seems to be involved in the process of its uptake in cancer cells (27). 18F-choline has been shown to have a greater sensitivity and accuracy than 18F-FDG PET/CT to detect prostate malignancy: sensitivity 73% versus 31% and accuracy 67% versus 53%, respectively (28). A high Gleason score and rising PSA level have been shown to increase rates of detection of 18F-Choline PET/CT. One study found 18F-Choline PET/CT detected prostate cancer recurrence in 97% of patients with Gleason Score >7, 82% of patients with Gleason Score = 7 and 63% of patients with Gleason Score < 7. A total of 43% of patients in this study had recurrence in the prostatic bed, and 57% patients had local metastasis (29). Currently, it is not recommended to perform a Choline PET/CT with a PSA value <1 ng/ml (24). Also, Choline PET/CT has a low spatial resolution and is limited in the identification of small lymph node deposits.

1.2.3 Whole-body MRI

Recent advances in MRI have made it possible to image the whole body (Whole body-MRI (WB-MRI)) within a reasonable time of 50-60 minutes. Dynamic contrast enhanced (DCE) and diffusion weighted imaging (DWI) complement conventional anatomical MRI techniques and provide a combined approach assessing cancer anatomy, microstructure and function. This enables the study of extra-skeletal involvement, including lymph nodes and other soft tissue metastases (30,31). Also, WB-MRI is conducted without irradiation and so patients are not exposed to the cumulative radiation exposure of bone scan, plain films and CT which is more than several years of natural background radiation (23,32).

1.3 Biopsy of radiorecurrent cancer

Positive biopsies are currently the only way to confirm local relapse. However, it is well known that false-positive results can be observed due to difficulties in distinguishing radiation-induced atypia of benign glands from malignancy (33-35). Tumour resolution after radiotherapy has no identifiable glandular morphology, and these remnants can be given a high Gleason score (33). Post radiotherapy prostate biopsies should be evaluated by a pathologist who is familiar with these findings (35-37). The time after radiotherapy at which to perform prostate biopsy has been discussed previously. Crook et al. (33) showed that 34% of positive biopsies that are obtained 12 months after radiotherapy convert to negative status by 24-30 months, whilst about 20% of the patients who have a negative post treatment biopsy will later experience positive re-biopsy. Scardino (38) also demonstrated a similar rate of 32% of men with a positive 12-month biopsy result transitioning to negative by 24 months. False negatives have been put down to sampling error whereas false-positives and indeterminate biopsies also frequently occur due to delayed tumour regression (33). These ‘false-positive’ biopsies might be one of the reasons for over-diagnosing radiorecurrent prostate cancer (34).

Overall, these studies indicate biopsies should take place at least 24-36 months after radiotherapy.

1.3.1 Transrectal Ultrasound biopsy

Whilst transrectal ultrasound (TRUS) systematic 10-12 core biopsies are standard care, they have inherent inaccuracies as a diagnostic strategy. In the setting of radiorecurrent disease, these errors can equally lead to inappropriate therapeutic decisions. First, TRUS biopsies miss clinically significant disease that is present. Second, they miss-classify significant disease as insignificant. These two errors may lead a man being recommended to effectively undergo palliative care with expectant management and hormones rather than potentially curative local therapy. Third, TRUS biopsies detect small volume clinically insignificant disease which may inappropriately be attributed as the cause of biochemical failure (BF) when in fact micro-metastases are present. This could lead to unnecessary local salvage therapy which carry variable rates of complications and side effects.

1.3.2 Transperineal biopsies

Transperineal template prostate mapping (TPM) biopsies have been shown to be more accurate in detecting both primary and radiorecurrent disease. TPM biopsies involve using a 5mm brachytherapy grid applied to the perineum and a transrectal ultrasound probe to visualise the prostate. Biopsy cores are taken every 5-10 mm with two biopsy cores taken in the same grid co-ordinate to cover mid-gland to base if the full length of the gland is not covered by one biopsy core. In a treatment-naive prostate gland, 5mm TPM has been shown to be a more accurate diagnostic method when compared with current standard TRUS biopsy (39,40).

Multi-parametric MRI (mpMRI) using various combinations of T2-weighted (T2W), DCE-MRI, DWI has become more prominent in the (pre-biopsy)

diagnosis of prostate cancer. Indeed, mpMRI has been shown to accurately detect lesions in the prostate (41,42). After radiotherapy, prostatic tissue demonstrates diffuse low signal intensity on T2W MRI, with indistinct zonal anatomy and diffuse low T2 signal, which hinder tumour detection. DCE-MRI has been shown to have significantly better sensitivity (72 vs. 38%), positive predictive value (46 vs. 24%) and negative predictive value (95 vs. 88%) than T2W MRI (43).

MRI-targeted biopsies (MRI-TB) as well as whole-gland TPM biopsies have shown promising accuracy rates in identifying radiorecurrent disease (44,45). MRI-TB have been shown to have similar detection rates to TPM for clinically significant cancer detection in radiorecurrent setting: 84% vs 92%, respectively (45).

1.4 Whole-gland salvage therapy

Current whole-gland salvage treatments for radiorecurrent prostate cancer include radical prostatectomy (RP), brachytherapy, cryotherapy and High Intensity Focused Ultrasound (HIFU).

1.4.1 Salvage radical prostatectomy

Salvage radical prostatectomy (S-RP) has satisfactory oncological control with biochemical disease-free survival (b-DFS) of 31-69% at 5 years and at 30-43% at 10 years (46,47). However, this salvage method is not often performed due to the high risks of morbidity. Complications such as incontinence (10-80%), anastomotic stricture (17-32%) and rectal injuries (3.3-50%), stem from the fibrosis, merging of tissue planes used for dissection and poor wound healing caused by radiotherapy (36,48). Studies reporting these outcomes have all emphasised the importance of an experienced surgeon due to the high technical demand.

1.4.2 Whole-gland salvage brachytherapy

Several studies have shown good b-DFS rates with salvage brachytherapy for radiorecurrent disease. Grado et al. (48) examined salvage Brachytherapy in 49 patients and reported b-DFS at 3 and 5 years was 48% (95% CI 32-63) and 34% (95% CI 17-51), respectively. Disease specific survival was reported as 89% (95% CI 73-96), and 79% (95% CI 58-91), at 3 and 5 years respectively. Aaronson et al. (49) showed rates of 89.5% b-DFS at 3 years. Common complications include lower urinary tract symptoms, hesitancy, nocturia, rectal bleeding and frequent bowel movements. A serious complication is a prostatic-rectal fistula which in one study occurred in 12% of patients. These complications were found to be higher than those of salvage cryotherapy (50,51). Brachytherapy appears to be a potentially useful salvage therapy that needs further evaluation.

1.4.3 Whole-gland salvage cryotherapy

Salvage cryotherapy has shown good 5 year b-DFS (40-58 %), which can be up to 73% in patients who had low-risk disease prior to radiotherapy. It must be noted that these studies vary on their definition of BF (PSA >0.5 ng/ ml vs. ASTRO vs. Phoenix definition) (50-53). With improvements in technique and development of cryo-technology such as thermocouples that monitor the temperature at important sites within the prostate, and a urethral warming device used to prevent tissue sloughing, complication rates have improved although can still be high: incontinence 4-73%, recto-urethral fistula 0-3.4%, perineal pain 5.6-39.5% and urinary retention 0-67 % (50,51,54). Sloughing and urethral stricture rates have been reduced from 10 to 15% to as low as zero (52,55). Erectile dysfunction has not improved (72-86%).

1.4.4 Whole-gland salvage HIFU

Many studies have examined HIFU as a potential salvage therapy for radiotherapy failure cases. Murat et al. (56) treated 167 patients who had

radiorecurrent disease with salvage HIFU. Patients were separated into low, intermediate and high-risk groups based on pre-radiotherapy disease risk. The progression-free survival rate at 3-years was reported as 53%, 42% and 25%, respectively. Ahmed et al. (57) reported 1 and 2 year b-DFS rates of 62 and 48%, respectively, in patients who achieved a PSA nadir of <0.5 ng/ml. Overall, common complications include incontinence (10-50%), bladder neck stenosis (17%), retention due to urethral stricture (17%), erectile dysfunction 66.2-100% and recto-urethral fistula (3-16%) (58-60).

In summary, despite good oncological control, S-RP is not widely performed due to high morbidity. Brachytherapy, cryotherapy and HIFU are also used as salvage therapies, but their long-term oncological outcome is still unknown and the morbidity is still high. In primary therapy, these latter treatments are currently undergoing evaluation as part of tissue- preserving focal therapy strategies in which they target cancerous lesions in the prostate. Some early data suggest that a similar strategy could be adopted for radiorecurrent disease. The goal of these ablative therapies is the same: maximum destruction of cancerous tissue with minimal damage to critical surrounding structures such as the urethra, the urinary sphincter, bladder neck and the rectum (61). However, potential problems of focal therapy in radiorecurrent disease include accurately localising recurrent disease within the prostate, the margins of safe treatment which preserve oncological efficacy whilst minimising harms and strategies of follow-up. These problems are common to the focal therapy story in treatment naıve disease (62).

1.5 Location of radiorecurrent prostate cancer

There has been some debate on the multi-focality and location of radiorecurrent disease. Two studies conducted by Leibovici et al. (63) and Haung et al. (61) examined RP specimens in radiorecurrent disease. They showed that radiorecurrent disease is often bulky, high volume, bilateral (74%) and close to (67-74%) or involving the urethra (7%). They felt that as biopsies were not able to accurately detect radiorecurrent disease, focal

therapies may miss important areas of cancers that could lead to progression and metastatic spread.

Haung et al. (61) found that in 46 RP specimens, 90% of cases had cancer foci at the apex. A further 28% of specimens in this study also had multi-focal disease. However, other studies have shown that recurrence occurs at the initial cancer index lesion site (64,65). Cellini et al. (65) found that in 118 patients, areas not initially affected by tumour had no evidence of disease recurrence at a median of 45 months follow-up. There is a possibility that, if only one focus is treated, and multi-focal disease is present, these areas can develop and metastasise; however, it may be probable that the index lesion hypothesis may also be relevant in this setting (66,67). We have previously discussed the role of TPM biopsies and mpMRI in detection of localised recurrence—these modalities would in theory have the ability to provide three-dimensional data to drive the focal delivery of ablative modalities.

1.6 Focal Salvage Therapy

This would involve delivering treatment to a localised area of the prostate sparing treatment to the rest of the gland thereby minimising further nerve damage and potentially reducing risk of bowel related injury.

1.6.1 Focal Salvage brachytherapy

There are limited studies on focal salvage brachytherapy, however one study performed by Peters et al. (68) examined 20 patients who underwent focal salvage brachytherapy post primary EBRT. Inclusion criteria for this study encompassed that patients had to have biochemical failure > 2 years after initial radiation treatment, with TRUS biopsy proven unilateral recurrence that was in concordance with MRI findings, no lymph node or metastatic disease and no ADT treatment at time of salvage therapy. Median follow up was 36 months where toxicity and PSA follow up was evaluated. Biochemical failure was defined according to the Phoenix definition (PSA nadir + 2.0 ng/ml). 30%

of patients were reported to have not responded to treatment either due to biochemical failure (n=3) or progression of metastatic disease (n=3). 3-year b-DFS estimates were 60% and 71% including and excluding non–responders. Incontinence occurred in four patients, urethral stricture in one patient and radiation cystitis in another. Only rectal pain was reported though it is unclear how many patients suffered this. No rectal fistula was reported and of five patients' potent pre-op, four patients maintained their potency and one patient reported a slight decrease, but did not require any further therapy.

1.6.2 Focal salvage cryotherapy

Eisenberg et al. (69) performed a retrospective study on 19 patients. These patients were selected on the basis that they fulfilled Phoenix definition for BF and had TRUS biopsy confirmed recurrence: the recurrence was unilateral and their glands were only partially treated with cryotherapy. Fifteen men had 6 months' follow-up which included 3 monthly PSA and TRUS biopsy. The complication rates in this study were low with one patient developing mild stress urinary incontinence, one developed a urethral stricture that required dilation and one developed a prostatic urethral ulcer managed with supra-pubic catheter drainage with resolution after 6 months; whether this represented a fistula was difficult to determine from the study report. Only 5 patients had available potency data with 2 men maintaining potency and 3 were impotent after treatment. Using the Phoenix definition of failure, 89%, 79% and 79% of men were free of biochemical recurrence at 1, 2 and 3 years, respectively. Although 19 men were included, only 10 men were re-biopsied with 90% having no recurrence at 1 year biopsy. Overall, this was a small study with limited and poor follow-up. Although b-DFS rates appear to be high, not all patients were followed up and only half of these men had a biopsy post-salvage treatment.

1.6.3 Focal salvage HIFU

Ahmed et al. (70) performed focal salvage HIFU in 39 patients. Disease recurrence was confirmed by mpMRI and either TPM (20 men) or TRUS biopsies targeted to the area of recurrence (19 men). Focal HIFU was either hemi-ablation (ablation of the lobe up to urethra) or quadrant ablation (ablation of one half of the lobe anterior or posterior). Those patients with recurrence confirmed by TRUS biopsies underwent hemi-ablation. If there was multi-focal cancer, then the patient underwent index lesion ablation if the untreated areas had 1 core or less with 3 mm or less of maximum 3 + 3 disease (on TPM) and/or no lesion on mpMRI. Median follow-up was 17 months. A total of 44% achieved a PSA nadir of <0.5 ng/ml, and the 1, 2 and 3-year b-DFS rates for this group were 86%, 75% and 63%, respectively, using Phoenix criteria. However, when biopsy post salvage was positive and requirement for ADT was included in the definition of failure, these rates decreased to 79%, 67% and 45%, respectively. For men who did not achieve PSA nadir less than 0.5 ng/ml (56%), the 1, 2 and 3 year b-DFS rates were much lower at 55%, 24% and 0%, respectively (70). Pad-free, leak-free continence status after treatment was 64%, and the pad-free rate was 87% as measured at last follow-up. Erectile function worsened with IIEF-5 scores decreasing from a median of 18-13 at 6 months. One patient developed a recto-urethral fistula and this resolved spontaneously after 6 months of supra-pubic catheter drainage and colostomy, as confirmed on repeat serial MRI studies, urethrograms and clinical symptoms.

1.7 Cost effectiveness of salvage therapies

There are several salvage therapies available and one important consideration is the impact on healthcare costs. As discussed earlier, the majority of patients who develop biochemical failure post radiotherapy, are placed on long term hormonal therapy (12-14). ADT has been shown to be more costly in both primary and salvage setting. Indeed, a longitudinal analysis performed by Wilson et al. (71) examined 171 patients who had been diagnosed with prostate cancer and had a primary treatment recorded.

Patients were classified according to D'Amico risk. ADT was found to have the highest cumulative cost over a 5.5-year period (71) compared with other prostate cancer therapies; ADT ($69,244 (£49,348)) vs. watchful waiting ($32,135(£22,902)), brachytherapy ($35,143 (£25,046)) and EBRT ($59,455 (£42,372)). This may be because higher D'Amico risk patients are treated with more costly therapies than those with lower risk disease who can be managed with watchful waiting. Despite this by the end of follow up, ADT and EBRT are the most costly therapies.

Boyd et al. (72) created a model to compare salvage cryotherapy with immediate ADT and compared with 20% deferred ADT – i.e. patients not immediately started on ADT. All patients had biopsy proven radiorecurrent disease with no evidence of metastases. The study found that salvage cryotherapy was markedly cheaper over patients' lifetime by £29 719 (€37 619) compared with 20% deferred ADT with a mean Quality-Adjusted life years (QALY) gain of 0.68 (95% CI 0.4 to 1.04) versus 0.56 (95% CI 0.28 to 0.87), respectively. There was an even greater average cost of starting ADT immediately compared with salvage cryotherapy of £100 914 versus £62 150.

1.8 Conclusion

With up to one-third of men undergoing curative radiation therapy for localised prostate cancer demonstrating biochemical failure within 5-8 years, there is a clinical need to find local curative salvage therapies. Salvage treatment is compromised by the irradiated pelvis, resulting in increased treatment toxicity. Although radical prostatectomy has good oncological outcome, it is not often performed due to the high technical skill required to avoid significant complications. Whole-gland salvage ablative therapies have improved resulting in decreased complication rates; however, their long-term oncological outcome is still not available and substantial side effects can still occur.

Through improved methods of detection, including frequent PSA measurements, mpMRI and targeted image-guided prostate biopsy, as well

as novel imaging which may detect micro-metastatic cancer, those with radio-recurrent disease could be better identified. As recurrent disease is better localised focal salvage ablative treatments may have a role. Studies examining these types of treatment show early signs that toxicity may be less compared to whole-gland salvage approaches. There is an urgent need for large, prospective studies involving focal salvage ablative treatments to evaluate benefits and risks and provide medium and long-term cancer survival outcomes.

Chapter 2 Hypotheses

In this chapter, the hypotheses of the research study will be set out with the objectives. The methodology of the trial will then be discussed.

As discussed above, there is a need for accurate re-staging of radiorecurrent prostate cancer, precise intra-prostatic recurrent disease localisation and feasibility of focal salvage treatments.

The hypotheses are therefore:

1) Whole body MRI has a greater sensitivity for the detection of metastases in patients with radio-recurrent prostate cancer compared to Choline PET/CT and bone scan.

2) Abnormalities seen with multi-parametric MRI are associated with clinically significant prostate cancer in the radio-recurrent prostate cancer setting.

3) The conduct of focal salvage therapy in men with radiorecurrent prostate cancer is both feasible and acceptable.

In order to answer the above hypotheses, the FORECAST – FOCal RECurrent Assessment and Salvage Treatment - Study was set up. (Please see attached protocol in Appendix 10.1)

FORECAST is a prospective, multi-centre, diagnostic and therapeutic, investigator-led study. It is a prospective cohort validating study conforming to level I evidence for diagnostic test evaluation and conforming to Idea, Development, Exploration, Assessment, Long-term Follow-up, Improving the Quality of Research in Surgery (IDEAL) guidelines stage 2b evaluation study for assessment of focal salvage therapy (73). Monitoring of subject safety and study compliance is being managed by Data Monitoring and Trial Steering

Committees, comprising an impartial (medically qualified) chairperson, the co-chief investigators, study coordinator, principal investigators from each study site, study statistician, and two patient representatives. The trial is registered with ClinicalTrials.gov identifier NCT01883128. The study has also been awarded National Cancer Research Network (NCRN) approval.

2.1 Study Objectives

2.1.1 Primary Objectives

1. To evaluate the accuracy of whole-body MRI to detect and rule-out regional lymph node and distant metastatic prostate cancer in men with biochemical recurrence following radiotherapy.

2. To evaluate the accuracy of multi-parametric MRI targeted prostate biopsies in identifying areas of radiorecurrent prostate cancer compared to transperineal template prostate mapping biopsies.

3. Presence of urinary incontinence (any pad usage plus any leakage of urine) as determined by the UCLA Expanded Prostate Cancer Index Composite (UCLA-EPIC) urinary continence questionnaire, at 12 months, in those men with no urinary incontinence at baseline.

2.1.2 Secondary objectives

1. To determine the complications and side-effect profile of focal salvage therapy to treat localised radiorecurrent prostate cancer.

2. To provide preliminary data on short term disease control outcomes after focal salvage therapy (PSA kinetics, imaging evidence of localised recurrence, rate of ADT and metastases/death).

2.2 Study population

Eligibility criteria for the trial primarily include men who have had previous external beam radiotherapy or brachytherapy with or without neo-adjuvant/adjuvant hormone therapy. Biochemical failure as defined by the Phoenix criteria (PSA nadir + 2 ng/ml).

See Appendix 10.1 for trial protocol with full inclusion and exclusion criteria.

2.3 Imaging

If the patient consents to the trial they will have a series of imaging tests (Choline PET/CT-CT, radio-isotope bone-scan if not already carried out in the last 6 months), mpMRI Pelvis/prostate and whole-body MRI (See below Flowchart 1 – FORECAST Study).

Table 1 compares the standard care and index tests for localised and distant disease. Importantly, for each comparative analysis (WB-MRI versus standard staging tests; MRI-targeted biopsies versus TPM-biopsies) all men who are considered likely to benefit from having these tests will have both the index test and reference test relevant for each comparison; this will minimise the selection bias in a manner that reflects the clinical imperative. In other words, if initial tests show evidence of metastatic disease these men will not be included for further tests as it is considered that men with metastatic disease experience more harm from further invasive tests such as TPM-biopsies. This exclusion reflects the clinical standard and thus selection bias is minimised. To minimise any expectation bias clinicians reporting WB-MRI and pelvic/prostate mpMRI will be blinded to the result of the other. They will however have equal access to previous patient details such as PSA, previous biopsy results at initial diagnosis prior to radiotherapy, previous radiotherapy details and use of neo-adjuvant/adjuvant hormones, in order to pragmatically reflect standard practice. A bone biopsy will be performed if WB-MRI was positive and Choline PET/CT and bone-scan were negative. This decision would be by discussion at a multidisciplinary team meeting. This would ensure

that patients who are found to have a negative bone biopsy and presumed negative for metastatic disease can continue to have focal salvage treatment provided they have local positive disease on prostate targeted or TPM biopsy. Also, a repeat whole-body MRI at 12 months will be performed in all men as part of a further study LOCATE — Localising Occult prostate Cancer metastasis with Advanced imaging Techniques ClinicalTrials.gov Identifier: NCT02935816. This will be able to determine whether temporal changes (in response to surveillance or to therapy) allow lesions on WB-MRI which are not spotted on standard BS and Choline PET/CT to be concluded as malignant. If shown to have a better sensitivity and specificity compared to current diagnostic tools used in recurrent prostate cancer, this gives rise to the potential of introduction of WB-MRI as a single test or complementary to one or both of Choline PET/CT and bone-scan. This may allow patients to be accurately identified for further treatment appropriately without having the burden of several scans and without exposure to further irradiation. Patients will remain blinded to the results of the index tests under evaluation until after the appropriate reference test has been conducted. Patients will be excluded from analysis if they are withdrawn from the study or unable to undergo the reference test after one of the index test, or are unable to have focal salvage therapy.

2.4 Transperineal template prostate mapping biopsy

This will be carried out under general regional anaesthetic or local anaesthetic with sedation. The patient will undergo 12 zone sampling using a modified version of that described by Barzell et al. (74) (See Figure 1– Transperineal Prostate Mapping Modified Barzell Zones below). MRI cognitive targeted sampling will also be taken. This is performed by comparing the pre-intervention mpMRI to the live intra-operative prostate ultrasound on two different screens (cognitive or visually targeted).

Patients who have the following will not be eligible to have focal salvage therapy and thus will be withdrawn from the study and returned to standard care:

- Men in whom the TPM-biopsies were inadequate for analysis due to lack of complete gland sampling
-Men unfit to undergo focal salvage therapy subsequent to TPM-biopsies.
- Men unwilling to undergo focal salvage therapy
- Bulky bilateral disease that would require whole gland treatment.

2.5 Treatment

The decision between focal cryotherapy or HIFU salvage ablative methods will be based on the location of recurrent disease. Patients are more likely to undergo HIFU if the tumour is posterior and/or apical and men will be advised to have cryotherapy if the tumour is predominantly anterior. This is to ensure optimum energy delivery as HIFU can often not deliver energy in the upper parts of the prostate whilst the cryoprobes can be placed directly into the area of the tumour. The decision in those which are basal-middle and posterior will be pragmatically chosen by physician and patient as would happen in standard care.

2.6 Focal salvage treatment

The treatment will cover the side of the gland in which the clinically significant lesion(s) have been identified by a combination of MRI and biopsy as follows.

The following broad rules will be followed in order to standardise the therapy (See Figure 2- Types of focal therapy):

- Tissue will be ablated in the entire affected quadrant of the prostate provided that less than one half of the lobe is affected.

- Treatment will reach the urethra and may cross the midline by up to 5-10 mm if the disease is close to the midline (minimum 5 mm margin over midline) or crosses over (minimum 10 mm margin over midline) (anterior or posterior ‘dog-leg’), provided that the treatment does not cross the para-sagittal plane on that side (usually 10 mm from midline).

- At least one neurovascular bundle must be avoided by ensuring a minimum distance of ablation zone to contralateral neurovascular bundle of 10 mm. This would usually require preservation of the contralateral lobe but the 10mm rule ensures that in patients in whom the dog-leg is used the contralateral neurovascular bundle avoids damage.

- When cancer is seen at the overlapping or going into the apical sphincter on mpMRI the patient should be excluded.

- In men in whom both lobes meet criteria for clinically insignificant cancer (≤3 mm and absence of Gleason pattern 4), the lobe with the dominant disease burden will be treated. This will be evaluated primarily on biopsy results. If these show identical bilateral disease burden, the side with the highest score for probability of malignancy on mpMRI will be treated. If this is also equivalent, a second re-view of the biopsies will be requested by the trial pathologist and the dominant side treated. Only those patients with exactly equivalent disease bilaterally following these three reviews will be excluded from the trial.

2.7 Follow-up

This will take place at 4 weeks, 3 months, 6 months, 9 months and 12 months' post-treatment. At each follow-up appointment, the patient will have either a telephone consultation or clinic visit to discuss their results and review any adverse events using National Cancer Institute Common Terminology Criteria (NCI CTC) classification system. They will be asked to fill patient reported validated questionnaires International Prostate Symptom Score (IPSS), IPSS Quality of Life (QoL), UCLA-EPIC Bowel Questionnaire, erectile dysfunction, the International Index of Erectile Function (IIEF)-15 questionnaire to assess any change in urinary, bowel or sexual function and a PSA blood test. At 12 months, the patient will have mpMRI to see if there is any evidence of residual disease. If post treatment, there is a PSA doubling time of less than 3 months or fails by PHOENIX/ASTRO Definition (PSA nadir

+ 2 ng/ml). The patient will undergo repeat prostate mpMRI and if warranted repeat mpMRI targeted biopsy+/staging scans (Choline PET/CT/Bone Scan).

Table 1 - Study diagnostic procedures

Standard care	**Index Tests under evaluation**
Distant Disease	**Distant Disease**
Bone Scan Choline PET/CT +/- pelvic lymphadenectomy +/- bone or tissue biopsy	Whole-body MRI
Local Disease	**Local Disease**
TPM Biopsies	Multi-parametric MRI-targeted biopsies

2.8 Flow Chart 1 – FORECAST Study

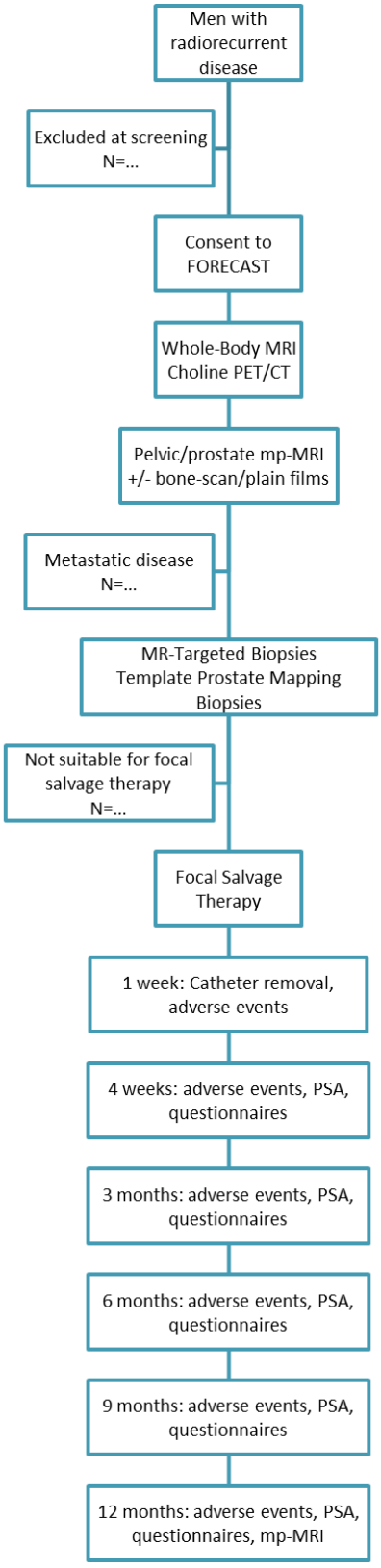
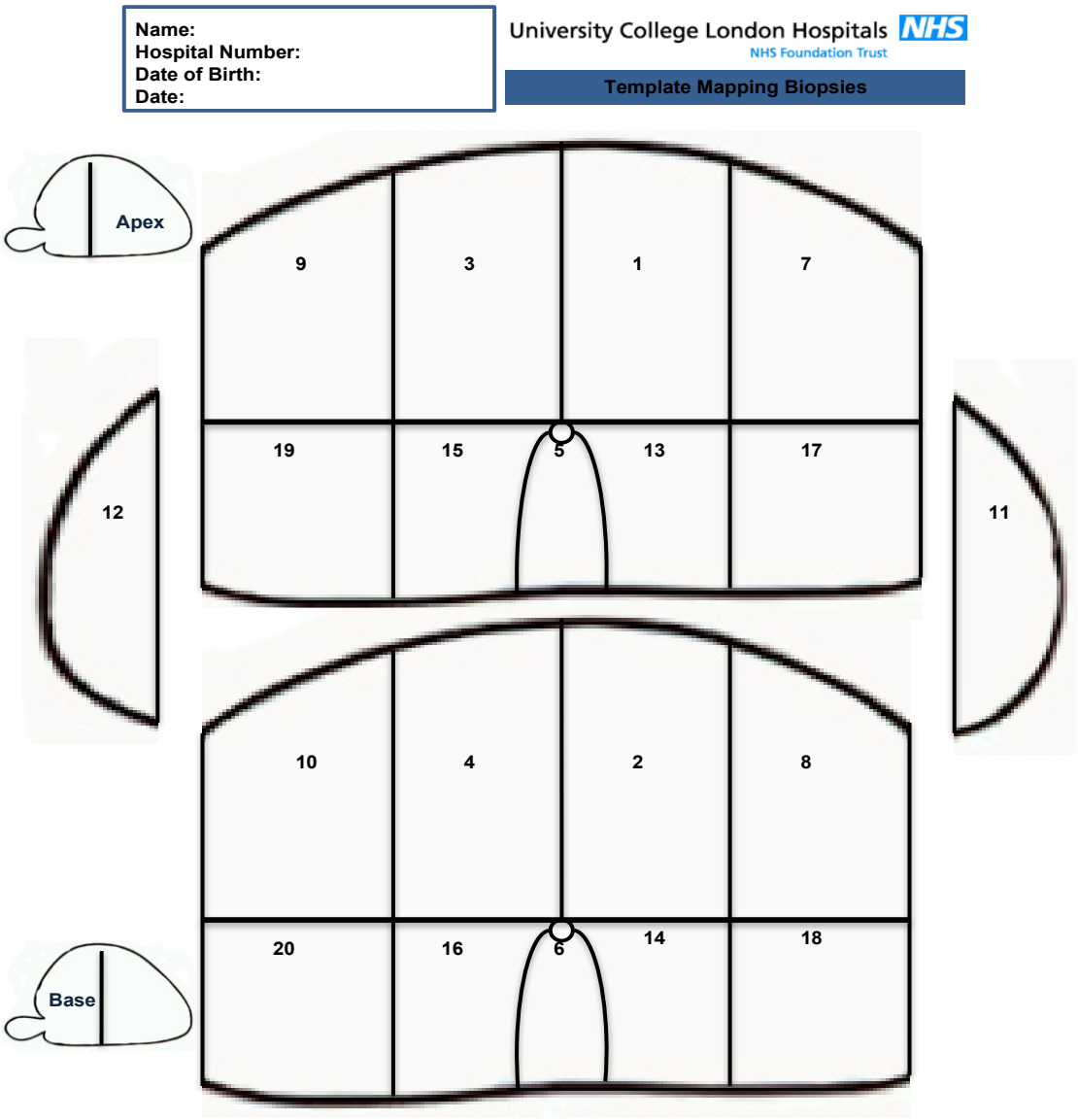


Figure 1 – Transperineal Prostate Mapping Modified Barzell Zones



Modified Barzell Zones

1 Left Parasagital Anterior Apex
2 Left Parasagital Anterior Base
3 Right Parasagital Anterior Apex
4 Right Parasagital Anterior Base
5 Midline Apex
6 Midline Base
7 Left Medial Anterior Apex
8 Left Medial Anterior Base
9 Right Medial Anterior Apex
10 Right Medial Anterior Base
11 Left Lateral
12 Right Lateral
13 Left Parasagital Posterior Apex
14 Left Parasagital Posterior Base
15 Right Parasagital Posterior Apex
16 Right Parasagital Posterior Base
17 Left Medial Posterior Apex
18 Left Medial Posterior Base
19 Right Medial Posterior Apex
20 Right Medial Posterior Base

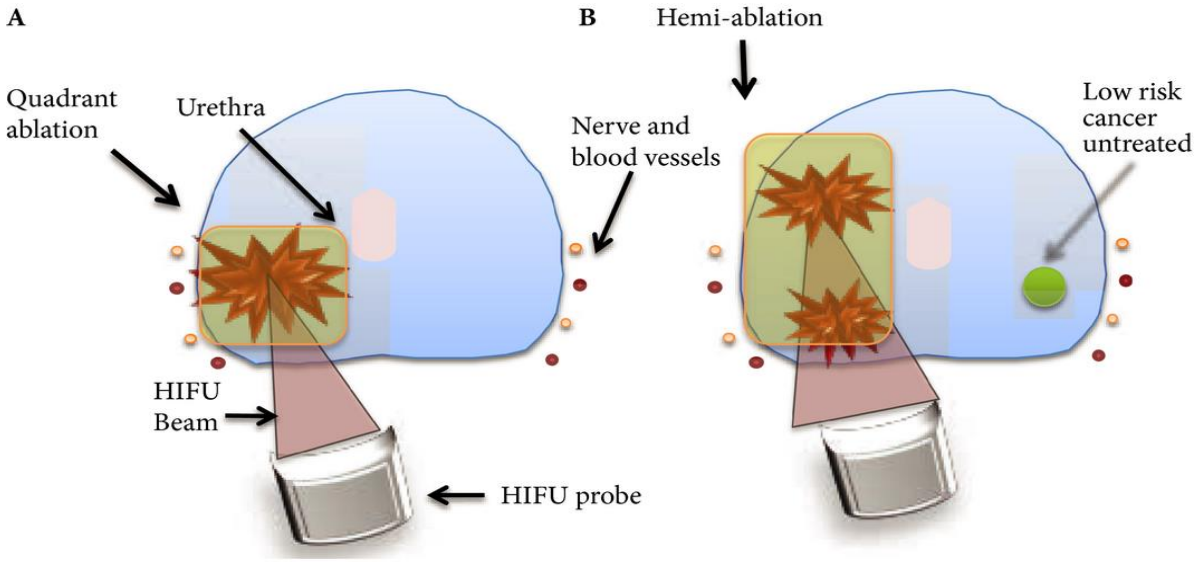
HGPIN / atypical acini

Clinically insignificant disease (G3+3 up to 3mm)

Gleason = 3+4 AND/OR Max Cancer length 4-5mm

Gleason >/= 4+3 AND/OR Max cancer length >/=6mm

Figure 2 - Methods of focal ablation (A) Posterior quadrant salvage ablation to a single lesion with focal salvage high-intensity focused ultrasound (HIFU). (B) Hemi-ablation of index lesion to two index lesions with focal salvage HIFU whilst leaving low-risk cancer untreated.



Chapter 3 Imaging techniques for diagnosing radiorecurrent prostate cancer

This chapter includes two analyses examining diagnosis of distant metastases in suspected radio-recurrent prostate cancer. The first is a retrospective registry analysis comparing Bone Scan to Choline PET/CT. The second is a prospective analysis of WB-MRI vs. bone scan and Choline PET/CT from the initial results of the FORECAST Trial.

3.1 Choline PET/CT VS. Bone Scan in detection of radio-recurrent prostate Cancer

3.1.1 Introduction

Radiation therapy for prostate cancer is a common treatment. However up to 50% of patients can develop biochemical recurrence within ten years of primary radiation treatment (3-8). For men to be appropriately selected for further salvage treatment, metastatic disease should be ruled out and localised radiorecurrent disease should be identified accurately. Common sites of distant prostate cancer metastases are bone, lymph nodes, liver and lung (22). Current methods of detection of distant metastases are bone scintigraphy (BS) and Choline PET/CT.

3.1.1.1 Bone Scan

Bone is the first site of relapse in more than 80% of cases (20) following primary treatment of prostate cancer. BS however is known to have high rate of false positives resulting from trauma, degenerative change and inflammation. Bone scan is also limited by its ability to detect metastases at a low level of PSA. Previous European Association of Urology (EAU) guidance has advised that bone scan has no additional diagnostic value unless PSA serum levels are >20 ng/ml or the PSA velocity is >2 ng/ml per year (75).

3.1.1.2 Choline PET/CT Scan

As discussed above in Section 1.2.2, there are several different radiotracers used in the detection of recurrent and metastatic prostate cancer. Studies have found varying rates of detection between different radio tracers. Fricke et al. (76) compared 11C-acetate with 18F-FDG tracer and found that 11C-acetate had a higher detection rate of primary and recurrent prostate tumours than 18F-FDG (75% vs. 43%). However, it had a lower rate of detection of distant metastatic disease (50% vs. 75%) (76). Choline PET/CT also has a low spatial resolution and is limited in the accurate delineation of intra-prostatic recurrence. Currently, it is not recommended to perform a Choline/PET with a PSA value <1 ng/ml (24).

3.1.2 Aim

Our aim was to assess the concordance between Choline PET/CT and bone scan for metastatic radiorecurrent prostate cancer.

3.1.3 Methods and Materials

A retrospective registry analysis identified 97 men who underwent bone scan and Choline PET/CT scan (January 2010 to December 2014). Inclusion criteria consisted of men that had undergone previous radiotherapy or brachytherapy who underwent both bone scan and Choline PET/CT. Men were excluded from analysis if they were on hormones at the time of imaging.

Imaging protocol

Choline PET/CT

Patients were injected with either 18F-FECH/18F-FDG tracer. Whole-body PET/CT images were acquired 60 min after tracer injection. At approximately 90 min, a limited (one bed position, PET/CT) pelvic view was obtained with the prostate in the field of view. The CT acquisition parameters include: scout 120 kVp, 10 mA; CT 140 kVp, 80 mA, 0.8 s, pitch 1.75; CT slices 5 mm (70-cm FOV PET AC), 2.5 mm (50-cm FOV Std), 2.5 mm (50-cm FOV Lung). PET

acquisition parameters were 3D attenuation-corrected and non- attenuation-corrected images, 20 subsets with iterative reconstructions. CT images were then used to produce attenuation correction values for PET emission reconstruction and fused PET/CT presentation.

Bone-scan +/- plain radiography

Bone scans were performed using Technetium-99m labelled diphosphonates administered through intravenous injection. These diphosphonates chemically bond on the surface of hydroxyapatite crystals on the surface of bone such that the images represent local osteoblastic activity. Whole body imaging was performed with anterior and posterior views, 256 x 1024 matrix and energy window(s) of 140 KeV. Effective dose (ED) is 3mSv (or 5mSv for cancer patients) and Diagnostic Reference Level (DRL) is 600 MBq (0r 800 for cancer patients).

Statistical Analysis

Statistical analysis was performed using SPSS version 23.0 (SPSS, IBM Corporation, New York) and the R language environment (R Core Team 2015, version 3.2.1). SPSS was used for descriptive statistics and the rms package in R for the modelling process.

Using univariable and multivariable logistic regression, odds radios (ORs) with 95% confidence intervals (95% CIs) were obtained to assess the influence of clinical characteristics on the outcome of Choline PET/CT positivity. A two-tailed $p < 0.05$ was considered statistically significant. Factors with $p<0.05$ were retained in the final model.

Cohen's Kappa Score is useful for either interrater or intrarater reliability testing. The score can range from −1 to +1, 1 represents perfect agreement between the raters and 0 represents the amount of agreement that can be expected from random chance (77). Typically, it is accepted that values ≤ 0

indicate no agreement and 0.01–0.20 as none to slight, 0.21–0.40 as fair, 0.41– 0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as almost perfect agreement (77).

3.1.4 Results

Mean age at time of imaging was 69.4 years (SD 6.1). Patients were classified as low 6% (5/97), intermediate 30.9% (30/97) and high-risk disease 49.5% (48/97) (n=14 missing) according to D'Amico classification at baseline prior to external beam radiotherapy (EBRT). 91.8% (89/97) had external beam radiotherapy, 5.7% (6/97) had brachytherapy, 2.1% (2/97) had external beam radiotherapy with HDR brachytherapy boost. Radiation doses of 74 Grays in 37 fractions were the most common (n=11). Time from radiotherapy to biochemical failure was an average (±SD) of 66 months (±35). Median PSA nadir post radiotherapy was 0.30ng/ml (IQR 0.1-0.8) and median PSA pre-imaging was 4.80 ng/ml (IQR 2.7-7.3). (See Table 2)

Table 2 – Baseline Demographics

Baseline Demographics	
Age at time of referral years (Mean ±SD)	69.4 (±6.1)
Risk Catergory pre original Tx	
High-risk: PSA >20, G >8, T2c-3a (N %)	48 (49.5)
Intermediate risk: PSA 10 - 20, G7, or T2b (N %)	30 (30.9)
Low risk: PSA <10, G <6, T1-2a (N %)	5 (5.2)
PSA Nadir (Median)	0.3 (0.1-0.8)
PSA at time of scan (Median IQR)	4.8 (2.7-7.3)
Time between BS and BF months (Mean ±SD)	9.2 (±13.2)

Time between BF and CPET months (Mean ±SD)	9.3 (±13.2)
Time between BS and CPET days (Mean ±SD)	17.2 (±19.6)

Table 3 - Rates of Bone Scan Detection

Bone Scan Result	Frequency (%)
Negative	79 (81.4)
Positive	3 (3.1)
Equivocal	15 (15.5)
Total	97 (100.0)

Bone scan was positive in 3.1% (3/97), equivocal in 15.5% (15/97) and negative in 81.4% (79/97). (See Table 3) Sites of bone metastases (according to bone scan) included the pelvis 22.2% (4/18), spine 33.3% (6/18), lower limb 11.1% (2/18) and ribs 27.8% (5/18) One equivocal bone scan did not have site recorded (5.6% 1/18).

Table 4 - Rates of Choline PET/CT Scan Detection

	Choline PET/CT Positive	Choline PET/CT Positive Local	Choline PET/CT Positive Nodes	Choline PET/CT positive metastatic disease
	Frequency (%)	Frequency (%)	Frequency (%)	Frequency (%)
No	26 (26.8)	37 (38.1)	79 (81.4)	89 (88.7)
Yes	71 (73.2)	60 (61.9)	18 (18.6)	5 (5.2)
Equivocal				3 (3.1)

Total	97 (100.0)	97 (100.0)	97 (100.0)	97 (100.0)

Table 5 - Site of Choline PET/CT Metastases

Site of Choline PET/CT Metastases	Frequency (%)
Bone (5 positive 1 equivocal)	6 (75)
Tissue (both equivocal)	2 (25)
Total	8 (100)

Choline PET/CT was positive in 73.2% (71/97) and negative in 26.8% (26/97). Choline PET/CT scan was positive for local disease only in 48.5% (47/97), nodal disease only in 9.3% (9/97), and metastatic disease only in 2.1% (2/97). Choline PET/CT was positive in both local and nodal disease in 7.2% (7/97), in local and metastatic cases 1.0% (1/97) and in local, nodal and metastatic disease in 2.1% (2/97). Choline PET/CT was positive for local and equivocal for metastatic disease in 3.1% (3/97). Choline PET/CT was negative in 26.8% (26/97). Cumulatively, Choline PET/CT scan was positive for local disease in 61.9% (60/97), for nodal disease in 18.6% (18/97) and metastatic disease in 5.2% (5/97). Choline PET/CT was equivocal for metastatic disease in 3.1% (3/97). (See Tables 4&5)

In patients where bone scan was positive (3/97), 66.7% (2/3) were classified as high risk according to D'Amico at baseline, in the third patient, there was not enough baseline data to classify according to D'Amico risk. In patients with an equivocal score (15/97), 40% (6/15) patients classified as high risk and 53.3% (8/15) patients were classified as intermediate risk according to D'Amico at baseline. In one case baseline risk information was not available. In patients with positive bone scan, median PSA at time of imaging was 4.53ng/ml (range 2.35-6.70ng/ml). Median PSA in patients with equivocal bone scan was 4.95ng/ml (range 1.70 - 9.10ng/ml).

Of patients with positive local disease on Choline PET/CT scan (60/97) 55.8% (29/60), 40.4% (21/60) and 3.8% (2/60) were classified as high, intermediate

and low risk at baseline according to D'Amico score (baseline information missing in 8 patients). Of patients with positive nodal disease on Choline PET/CT scan (18/97), 61.1% (11/18) were high risk and 22.2% (4/18) were intermediate risk at baseline according to D'Amico score (baseline information missing in 3 patients). For patients with positive metastatic disease on Choline PET/CT, 60% (3/5) and 20% (1/5) were classified as high risk and low risk at baseline respectively according to D'Amico classification (baseline information missing in 1 patient). Two of three patients who scored equivocal for metastatic disease, were intermediate risk at baseline (baseline information missing in one patient). Median PSA in patients who had positive local, nodal and metastatic disease on Choline PET/CT scan was 4.1ng/ml (range 0.89-21.59), 4.65ng/ml (range 2.35-9.10ng/ml) and 2.36 (range 2.35-10.15ng/ml) respectively. It should be noted that there were only 5 patients with likely positive metastatic disease. In patients with equivocal metastatic disease on Choline PET/CT, median PSA was 6.15ng/ml (range 5.90-6.40ng/ml).

Table 6 – Concordance between Choline PET/CT and bone scan for metastatic disease

	Choline PET/CT positive for metastatic disease				
Bone Scan positive for metastatic disease		No	Yes	Equivocal	Total
	No	74	3	2	79
	Yes	2	1	0	3
	Equivocal	13	1	1	15
	Total	89	5	3	97

Concordance between bone scan and Choline PET/CT occurred in only 3 cases, (kappa value 0.024). In three cases where bone scan was positive for metastatic disease, concordance with Choline PET/CT was present in only one case. Bone scan was equivocal in 15 cases, concordance was reached in one case, was positive in a further case and negative on Choline PET/CT for 13 cases (kappa value 0.14). Choline PET/CT was positive for metastatic bony disease in 5 cases. In one case, Choline PET/CT and bone scan was

concordant, in one case bone scan was equivocal and in three cases, bone scan was negative (kappa value 0.14). (See Table 6)

Table 7 – Concordance between Choline positive metastatic disease and bone scan positive and equivocal results combined

	Choline PET/CT positive mets			
	No	Yes	Equivocal	Total
Bone Scan positive	No	74	3	2	79
	Yes and Equivocal	15	2	1	18
	Total	89	5	3	97

When bone scan positive and equivocal results were combined (n=18) and compared with Choline PET/CT, only 2 cases were concordant (positive) with one case being equivocal and 15 cases being negative for metastatic disease (kappa vaule 0.13). (See Table 7)

Table 8 - Univariable and Multivariable analysis for Choline-PET positive

Determinant (missing)	Univariable OR (95% CI); p-value	Multivariable OR (95% CI); p-value
Age at referral (0)	1.07 (0.99-1.16); 0.10	NS
Time between RT and BF (15)	1.00 (0.98-1.01); 0.57	NS
PSA at RT (14)	0.99 (0.97-1.01); 0.44	NS
Overall Gleason score pre-RT (5)	1.30 (0.72-2.35); 0.39	NS
D'Amico risk score pre-RT (14) Intermediate vs low risk High risk vs low risk	 1.22 (0.42-3.52); 0.71 0.56 (0.08-3.72); 0.55	 NS NS
PSA-nadir post-RT (57)	1.62 (0.36-7.30); 0.53	NS

PSA at scan (32)	0.95 (0.83-1.10); 0.50	NS
Time between BS and BF (12)	0.98 (0.94-1.01); 0.18	NS
Time between BF and CP (13)	1.01 (0.98-1.03); 0.67	NS
Type of Choline (18F vs 18FDG) (0)	4.06 (1.32-12.48); 0.14	NS

In both univariable and multivariable analyses, no factors (PSA at EBRT, baseline D'Amico, PSA at imaging) had a significant outcome in predicting Choline PET/CT positivity. (See Table 8)

3.1.5 Discussion

3.1.5.1 Summary of results

There is poor concordance with bone scan and Choline PET/CT in the detection of metastatic disease following radiotherapy for prostate cancer.

Concordance between bone scan and Choline PET/CT occurred in only 3 cases, (kappa value 0.024). In three cases where bone scan was positive for metastatic disease, concordance with Choline PET/CT was present in only one case. Choline PET/CT was positive for metastatic bony disease in 5 cases. In one case, Choline PET/CT and bone scan was concordant, in one case bone scan was equivocal and in three cases bone scan was negative (kappa value 0.14) (See Table 5). As discussed above, the kappa score indicates the level of agreement between two reporters. Throughout this study, the kappa value was 0.01–0.20 indicating the agreement was none to slight (77).

3.1.5.2 Methodological Limitations

Limitations of our study include its retrospective nature and lack of histopathological confirmation of suspected metastases, and lack of a reference standard so no diagnostic accuracies can be performed, this is similar to other studies. PSA doubling time and velocity data was not collected which could have aided the univariable and multivariable analysis in predicting likelihood of positive Choline PET/CT. The median PSA at time of scans in our cohort was also low at 4.80 ng/ml (IQR 2.7-7.3) which could mean that true metastatic disease had not yet declared itself resulting in low detection rates. Also, further follow up PSA and repeat scans post treatment (systemic/local) data was not collected. This could have given further information on equivocal scan results.

3.1.5.3 Comparison with Existing Studies

There are few studies that perform a direct comparison of bone scan to Choline PET/CT for the detection of distant disease. A study performed by Picchio et al. (78) compared 11C-Choline PET/CT with BS in detecting bone metastases (BM) of 78 patients with biochemical progression after radical treatment for prostate cancer. Suspicious lesions were confirmed during either conventional follow up with computed tomography (CT), MRI and X-rays within 20 days (median 10 days; range 1–84 days) of BS or Choline PET/CT, or instrumental follow up with imaging performed to monitor patients' disease. Concordant findings were examined on both a patient and lesion based analysis.

Concordance occurred in 71% (55/78) patients. 33% (18/55) were True Positive (TP) and 67% (37/55) were true negative (TN). In the remaining 23 cases, findings were discordant. 21 were equivocal on BS that were TP on 11C-Choline PET/CT in 29% (6/21) patients, TN in 63% (13/21) and FN in 9% (2/21).

On a lesion based analysis, 56 lesions were reported. Concordance occurred in 50% (28/56) lesions and in particular: 75% (21/28) were TP lesions, 4% (1/28) were equivocal lesions, and 21% (6/28) were FN lesions. As for discordant findings, 11C-Choline PET/CT reported TN in 24 of BS equivocal findings and in 5 of BS false positive (FP) findings. 11C-Choline PET/CT was TP in 6 of 36 BS equivocal lesions and in 1 FN BS lesion. BS was TP in 17 FN bone metastases reported on11C-Choline PET/CT and TN in a single FP case of 11C- Choline PET/CT rib lesion.

As there were a high number of equivocal lesions in the study, this resulted in the analysis being performed twice to allow for equivocal to be reported as positive and negative resulting in ranges of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy for 11C-Choline PET/CT 89–89%, 98–100%, 96–100%, 94–96% and 95–96%, versus BS 100–70%, 75–100%, 68-–100%, 100–86% and 83–90%, respectively. These high rates of detection could be due to an insufficient histopathological reference standard. In this study the mean free serum PSA level was 21.1 ng/ml (range 0.2- 500.0 ng/ml) compared to the current study where PSA was 4.80 ng/ml (IQR 2.7-7.3). This could be a reason for higher rates of metastatic disease within this Picchio's study.

Choline PET/CT also has the limitation of higher detection rates with a higher PSA level. Chondrogiannis et al. (7) examined the use of 18F-choline in detection of radiorecurrent disease and reported a detection rate of 54.5 % in patients with PSA levels between 1.0 and 2.0 ng/ml, 81 % with PSA level between 2.0 and 4.0 ng/ml, 89 % with PSA between 4 and 6 ng/ml and 100 % with PSA >6.0 ng/ml. Ceci et al. (4) reported on the performance of 11C – Choline in radiorecurrent disease and found a significant correlation between PSA kinetics and site of recurrence. In the detection of bony metastasis, PSA doubling time (PSAdt) and PSA Velocity (PSAvel) had an odds ratio (OR) of 0.968 (95% CI 0.906 - 1.034, p =0.032) and 1.043, (95% CI 1.01 - 1.07, p =0.01) respectively. For positive lymph nodes, this was 0.876 (95% CI 0.793 - 0.968, p =0.009) for PSAdt and 1.022 (95% CI 0.99 - 1.03, p =0.033) for PSAvel. Also within this study, patients with at least one site of Choline uptake, PSA was

9.08 ng/mL (median 5.1 ng/mL, range 2 – 60 ng/mL) compared to patients with negative results whose mean PSA level was 5.54 ng/mL (median 3.4 ng/mL, range 2 – 12 ng/mL, $p < 0.05$). Another study compared 11C-acetate with 18FDG tracer and found that 11C-acetate had a higher detection rate of primary and recurrent prostate tumours than 18FDG (75% vs. 43%). However, it had a lower rate of detection of distant metastatic disease (50% vs. 75%) (76).

Overall common problems with these studies are the lack of histopathological confirmation of distant metastases and low PSA values (typically less than 20ng/ml) when the scans are performed. The latter meaning PSA rise is likely due to the presence of micro-metastatic disease. Furthermore, these studies are retrospective in nature and typically examine a combination of patients following primary treatment of either radical prostatectomy or EBRT.

3.1.5.4 Clinical Implications

Our study has shown that concordance between Choline PET/CT and BS for the detection of radiorecurrent disease is low. BS has poor detection rates of metastatic disease at low PSA levels (median PSA at time of BS - 4.53ng/ml (range 2.35-6.70ng/ml).) Ultimately if Choline PET/CT can identify local, nodal and bone metastases at a lower PSA level, with lower rates of false positives it poses the question as to whether BS has a role in the detection of radiorecurrent prostate cancer. Especially as this further exposes a patient to unnecessary radiation.

3.1.5.5 Future Research

Further prospective studies should be performed to determine the clinical utility of BS and Choline PET/CT in diagnosis of radiorecurrent prostate cancer and whether any novel imaging can outperform these current standard of care tests. These imaging tests need to detect recurrent prostate cancer at low PSA levels <20ng/ml before metastatic disease is established.

3.1.6 Conclusion

There is poor concordance with BS and Choline PET/CT in the detection of metastatic disease following radiotherapy for prostate cancer. Further prospective trials examining emerging imaging techniques may be able to better characterize metastatic disease allowing men to be treated with the most appropriate salvage treatment.

3.2 Whole body - MRI vs. Choline PET/CT and Bone Scan in detection of radio-recurrent prostate Cancer

3.2.1 Introduction

Choline PET/CT and bone scan are common investigations used to investigate recurrent prostate cancer. Whilst BS is readily available, at low cost, it is anatomically imprecise and can have poor sensitivity and specificity for detection of metastatic disease in patients that have PSA <20ng/ml (75,79). Choline PET/CT has similar limitations and there is a wide use of radiotracers with differing detection rates as discussed above and no current recommended standard (24,80,81).

Whole-body MRI is a novel technique that may have a higher diagnostic accuracy than these current standards. It is now possible to perform whole body- MRI (WB-MRI) within a reasonable time of 50-60 minutes. Diffusion weighted imaging (DWI) and Dynamic contrast enhanced (DCE-MRI) complement conventional anatomical MRI techniques and provide a combined approach assessing cancer anatomy, function and microstructure. This allows for the examination of lymph node, soft tissue and bone metastases (30,31) without requiring ionizing radiation.
Indeed, the cumulative irradiation of CT, bone-scan and plain film radiography is more than several years of natural background irradiation (23). One of the drawbacks of bone scan is its inability to detect bone marrow metastases. Bone metastases are preceded by bone marrow metastases. Prostate cancer cells first seed into the normal haematopoietic marrow and its fat cells. This is followed by the activation of osteoblastic and osteoclastic cell lines, and the action of the former in particular, can be seen by bone scan (82). 18F-choline PET CT can detect bone marrow metastases due to the elevated uptake in cell proliferation. WB-MRI may detect prostate cancer cell masses in the normal haematopoietic marrow, before the bone marrow metastases are visible on bone scan (83).

3.2.2 Aim

Our aim was to assess the concordance between WB-MRI and Choline PET/CT and BS for the detection of metastases in radiorecurrent prostate cancer.

3.2.3 Methods and Materials

A prospective analysis from FORECAST study identified 50 men who underwent WB-MRI, BS and Choline PET/CT scan (April 2014 to September 2015).

Imaging protocol

Whole- Body MRI

3 Tesla scanner and a pelvic phased array receiver, with a pelvic coil. A full protocol of T1 and T2 weighted turbo-spin echo images, diffusion weighted images and a dynamic post gadolinium volume acquisition was used.

Choline PET/CT

As described above, Whole-body PET/CT images were acquired 60 min after tracer injection of either ^{18}F-FECH/18-FDG tracer. At approximately 90 min, a limited (one bed position, PET/CT) pelvic view was obtained with the prostate in the field of view. The CT acquisition and PET acquisition were as above and these were then reconstructed and fused to form PET/CT presentation.

Bone-scan +/- plain radiography

Technetium-99m labelled diphosphonates was administered through intravenous injection. Whole body imaging was performed with anterior and posterior views, 256 x 1024 matrix and energy window(s) of 140 KeV. Effective dose (ED) is 3mSv (or 5mSv for cancer patients) and Diagnostic Reference Level (DRL) is 600 MBq (0r 800 for cancer patients).

Statistical Analysis

Statistical analysis was performed using SPSS version 23.0 (SPSS, IBM Corporation, New York) and the R language environment (R Core Team 2015, version 3.2.1). SPSS was used for descriptive statistics and the rms package in R for the modelling process.

Using univariable and multivariable logistic regression, odds radios (ORs) with 95% confidence intervals (95% CIs) were obtained to assess the influence of clinical characteristics on the outcome of Choline PET/CT positivity. A two-tailed p <0.05 was considered statistically significant. Factors with p<0.05 were retained in the final model.

As above in Section 3.14 Cohen's Kappa Score is useful for either interrater or intrarater reliability testing.

3.2.4 Results

The mean age was 69.5 years (range 54-85; standard deviation 6.91). The median prostate-specific antigen (PSA) at the time of external beam radiotherapy (EBRT) was 14.7 ng/ml (interquartile range 7.78 - 36). Patients were classified as low 6% (5/48), intermediate 30.9% (30/48) and high-risk disease 49.5% (48/48) according to D'Amico classification at baseline prior to external beam radiotherapy (EBRT) (Missing baseline data in 2 cases). The most frequent EBRT dose given was 74 Gy over 37 fractions. Neoadjuvant/adjuvant hormonal therapy use was reported in 44 patients. The time from EBRT to biochemical recurrence was a median of 73 months (interquartile range 49.00-91.00). The time from EBRT to re-imaging was 78.9 (IQR 48.5-93.8). The median PSA at the time of imaging was 3.29 ng/ml (interquartile range 2.40-5.30) (See Table 11).

Table 11 – Baseline Demographics

Baseline Demographics	
Age at time of referral years (Mean ±SD)	69.5 ± 6.9
PSA at time of EBRT median (IQR)	14.7 ng/ml (interquartile range 7.78 - 36)
Risk Catergory pre original Tx	
High-risk: PSA >20, G >8, T2c-3a (N %)	36 (72)
Intermediate risk: PSA 10 - 20, G7, or T2b (N %)	8 (16)
Low risk: PSA <10, G <6, T1-2a (N %)	4 (8)
PSA Nadir Median (IQR)	0.3 (0.1-0.6)
PSA at time of scan Median (IQR)	3.29 (2.4-5.3)
Time between BF and restaging imaging months (Mean ±SD)	78.9 (±37)

WB-MRI identified local tumour in 52% (26/50) of cases. T3a disease was reported in only 1 case, with nodal disease being positive or equivocal in 6% (3/50) and 26% (13/50) of cases respectively. The commonest sites of nodal disease were external iliac (18%) and internal iliac nodes (8%). WB-MRI did not report any positive tissue sites for metastatic disease, rather, 4% (2/50) was equivocal and 72% (36/50) was negative, there was no report, for 24% (12/50) cases. WB-MRI was positive in 4% (2/50), equivocal 10% (5/50) and negative in 62% (31/50) for bone metastases.

Choline PET/CT was positive for local disease in 66% (33/50) of cases, and negative in 28% (14/50). T3a disease was reported in only 1 case. The commonest sites of nodal disease were external iliac 12% (6/50) and inguinal nodes 12% (6/50). Choline PET/CT reported two sites positive for tissue

metastases. Choline PET/CT was positive in 6% (3/50), equivocal 2% (1/50) and negative in 83% (43/50) for bone metastases. No report was given for 3 patients as to whether there was any positive/equivocal or negative for nodal disease.

Bone scan was positive and equivocal in 4% of cases (2/50) respectively.

Of 35 patients reported to have local tumour, concordance between WB-MRI and Choline PET/CT occurred in 20 cases Kappa score 0.311 (p=0.056). There were 7 cases that Choline PET/CT reported positive for local tumour when WB-MRI was negative and 3 cases where WB-MRI was positive for local tumour where Choline PET/CT was negative. (See Table 12)

Table 12 Concordance local tumour WB-MRI and CPET

		CPET Local Tumour Present		
		No	Yes	Total
WB-MRI Local Tumour Present	No	5	7	12
	Yes	3	20	23
Total		8	27	35

Of 19 patients where nodal status was reported. Concordance between WB-MRI and Choline PET/CT for NX-0 disease occurred in 14 cases Kappa score 0.548 (p=0.00032). There was one case reported as N1 disease on WB-MRI that was reported as N2 on Choline PET/CT. WB-MRI and Choline PET/CT were concordant in 4 cases for the same nodal site (external iliac node) kappa = 0.333 (p=0.121). However, in 4 other cases, sites reported by WB-MRI as positive for nodal disease, were not concordant with the same site on Choline PET/CT. (See Table 13 & 14)

Table 13 Concordance nodal disease WB-MRI and Choline PET/CT

		Choline PET/CT N Stage			Total
		N0	N1	N2	
WB-MRI N-Stage	0	1	0	0	1
	NX	1	0	0	1
	N0	12	1	0	13
	N1	0	2	1	3
	N2	0	0	1	1
Total		14	3	2	19

Table 14 Site of Nodal disease WB-MRI vs. Choline PET/CT

		WB-MRI Nodal Site 1				Total
		External Iliac	Internal Iliac	Common Iliac	Para-aortic	
Choline PET/CT Nodal Site 1	External Iliac	4	0	0	1	5
	Internal Iliac	1	1	1	0	3
Total		5	1	1	1	8

Of 35 patients where bony metastatic disease outcome was reported, concordance between WB-MRI and Choline PET/CT was achieved 30 cases. Of these 28 were negative on both WB-MRI and Choline PET/CT and positive in 2 cases. These were also positive for same site (thoracic and lumbar spine disease). 5 patients were reported as having equivocal disease on WB-MRI that was negative on Choline PET/CT (kappa score 0.411 $p<0.0001$) (See Table 15)

Table 15 Concordance of bony disease WB-MRI and CPET

		Choline PET/CT Bone Sites Outcome		
		Negative	Positive	**Total**
WB-MRI Bone Sites Outcome	Negative	28	0	28
	Equivocal	5	0	5
	Positive	0	2	2
Total		33	2	35

Concordance was achieved in only one case for bone metastatic disease between WB-MRI and Bone scan (kappa score 0.333 p=0.157). This was positive in same location (thoracic spine and left rib) (See Table 16).

Table 16 Concordance of bony disease WB-MRI and Bone Scan

		BS Bone Sites Outcome		
		Equivocal	Positive	**Total**
WB-MRI Bone Sites Outcome	Negative	1	0	1
	Positive	0	1	1
Total		1	1	2

Concordance was achieved in 2 cases where bony metastatic disease was detected on Choline PET/CT and bone scan (See Table 17). Of these cases, one was concordant in same area – thoracic spine, however in the latter case, the location was not reported on Choline PET/CT. However, there were two cases that were negative on Choline PET/CT and equivocal in Bone scan (Kappa = 0.333 (p=0.46)).

Table 17 Concordance of bony disease Choline PET/CT and Bone Scan

		BS Bone Sites Outcome		
		Equivocal	Positive	**Total**
Choline PET/CT Bone Sites Outcome	Negative	2	0	2
	Positive	0	2	2
Total		2	2	4

3.2.5 Discussion

3.2.5.1 Summary of results

Concordance between WB-MRI and Choline PET/CT for local disease occurred in 20/35 cases Kappa score 0.311 (p=0.056). Concordance between WB-MRI and Choline PET/CT for NX-0 disease occurred in 14/19 cases Kappa score 0.548 (p=0.00032). WB-MRI and Choline PET/CT were concordant in 4 cases for the same nodal site (external iliac node) kappa = 0.333 (p=0.121). However, in 4 other cases these tests were not concordant for sites of nodal disease (See Table 3 & 4). WB-MRI and Choline PET/CT was achieved 30/35 cases for bony metastatic disease (Kappa=0.411 (p<0.0001)). (See Table 5)

Concordance was achieved in only one case for bone metastatic disease between WB-MRI and Bone scan (kappa score 0.333 p=0.157). (See Table 6).

Concordance between Choline PET/CT and bone scan was achieved in 2 cases for bony metastatic disease (See Table 7). However, there was discordance in two cases that were negative on Choline PET/CT and equivocal in Bone scan (Kappa = 0.333 (p=0.46)).

Overall our study has shown that there is moderate agreement between WB-MRI and Choline PET/CT (Kappa score 0.548 (p=0.00032)) in the detection of NX-0 nodal disease and for bony metastatic disease (Kappa=0.411 (p<0.0001)) which was significant. There was fair agreement for bony metastatic disease detected by WB-MRI and BS (kappa score 0.333 p=0.157) and also for Choline PET/CT and BS (Kappa = 0.333 (p=0.46)) however significance was not achieved.

3.2.5.2 Methodological Limitations

Limitations include low PSA at time of imaging. The median PSA at the time of imaging was 3.29 ng/ml whilst this is important in the detection of early radiorecurrent disease to offer salvage treatments, determination of accuracy of WB-MRI was not possible as there were only 2 cases of metastatic disease. The other significant limitation was reporting of bone scan. Whilst bone scan reports as positive or equivocal when present, all other reports did not have definitive negative report thereby limiting analyses. If bone scans were recorded as negative, concordance between WB-MRI and Bone scan occurred in 18 cases – 17 negative, 1 positive (Kappa = 0.172 (p=0.186). WB-MRI reported 4 cases as equivocal and 1 case as positive that was negative on Bone scan. There was one equivocal result on bone scan that was negative on WB-MRI. Similarly, concordance between Choline PET/CT and bone scan occurred in 24 cases – 22 negative and 2 positive. One case reported as equivocal and one case reported as positive on Choline PET/CT were both negative on Bone scan. Two cases equivocal on bone scan were negative for bony disease on Choline PET/CT (Kappa = 0.440 (p=0.003).

3.2.5.3 Comparison with Existing Studies

Overall, we have shown that there was moderate agreement between WB-MRI and Choline PET/CT in the of detection of bony disease. There was also fair agreement between Choline PET/CT and bone scan for metastatic

disease. However these results must be interpreted with caution as there were limited cases of metastatic disease.

Other studies have also examined the concordance between WB-MRI and Bone scan. A study performed by An et al. (84) examined WB-MRI- Diffusion weighted imaging (WB-MRI-DWI), BS and PSA as predictors for bone metastases in prostate cancer – both primary and post ADT/EBRT (n=38). WB-MRI-DWI appeared to detect more spinal lesions than BS (24 vs. 19). Overall, however more metastatic lesions were detected by BS than WB-MRI-DWI (53 vs. 49).

A study performed by Barchetti et al. examined WB-MRI for the detection of metastases (85) in men wither treated with radical prostatectomy (n=82) or post EBRT (n=70) without hormonal treatment. WB-MRI had a sensitivity, specificity, PPV, NPV and Area Under Curve (AUC) of 99%, 98%, 98%, 96% and 0.971 respectively, for detection of bone metastases. For lymph node metastases, this was 98%, 99%, 97%, 98%, and 0.960 respectively. In this study 18FCholine-PET/CT was the comparative imaging technique and so detection differences between the two imaging investigations were not reported.

Conde-Moreno et al. (86) performed a similar study in 35 patients post primary treatment who were considering for salvage treatment. In this study however WB-MRI- DWI had a lower sensitivity, PPV, and NPV compared with Choline-PET/CT 44.93%, 86.11%, and 19.15%, vs. 97.10%, 93.06% and 77.78%, respectively. Specificity of WB-MRI-DWI was higher than Choline PET/CT 64.29% vs. 58.33%. The scans were concordant in seven patients and in three cases, a lesion was observed using WB-DW-MRI that was not detected with Choline-PET/CT. Choline-PET/CT detected lesions in 16 patients that were not observable using WB-MRI-DWI. However, a low kappa index score did not find consistency between the scans for bone (K index of 0.292 ($p = 0.003$)) or lymph node metastases (K index of 0.252 ($p = 0.001$)). 34.3% (12/35) patients remained the same staging. A change in metastatic staging occurred in 45.7% (16/35) patients went from being non-metastatic to

metastatic, 14.2% (5/35) being oligometastatic (<5 metastases) to be polymetastatic, 5.7% (2/35) went from being considered metastatic to M0. As a result of the outcomes of the WB-MRI-DWI and choline-PET/CT 65.7% (23/35) of patients, a different therapeutic approach was adopted.

A few studies have reported good sensitivity and specificity of WB-MRI compared with current imaging tools. LeCouvet compared DWI-WBMRI with BS/plain films and CT in 100 patients; 68 were felt to have metastases. The sensitivity of BS/plain films and WB-MRI for detecting bone metastases was 86 % and 98-100 %, respectively ($p < 0.04$), and specificity was 98 % and 98-100 %, respectively. The sensitivity of CT and WB-MRI for detecting enlarged lymph nodes was similar, at 77-82 % for both; specificity was 95-96 % and 96-98 %, respectively. The sensitivity of the combination of BS/plain films plus CT and WB-MRI for detecting bone metastases and/or enlarged lymph nodes was 84 % and 91-94 %, respectively ($p = 0.03$-0.10); specificities were 94-97 % and 91-96 %, respectively (23). Another study compared the detection rate of metastatic disease by WB-MRI to BS in 39 patients diagnosed with local prostate cancer. Interestingly, the sensitivity for detection of skeletal metastases for both BS and WB-MRI was 70 % (95 % CI 0.42-0.98), the specificity 100 % and the positive predictive value 100 %. WB-MRI and BS differed in the areas of detection. For instance, seven patients had bone metastases on BS and seven had skeletal metastases by WB-MRI, with concordant findings in only four. BS detected more rib metastases, whilst MRI identified more metastatic lesions in the spine (83). This study showed that WBMRI and BS have similar specificity and sensitivity, but may have to be used as complementary investigations to detect skeletal metastases from prostate cancer, rather than as alternatives.

Disadvantages however, include the cost of MRI and inability to be used in patients with metallic implants such as pacemakers or hip replacements. In the United Kingdom, sample costs for MRI may vary from up to £899 this is compared to CT up to £665 or bone scan up to £473.

The recognised limitations of these studies are that histology confirmation was not the reference standard because bone biopsies are not common practice and lymph node dissection is recommended only in patients who are suitable for further salvage therapy. These studies often had patients who had differing primary therapies either RP or EBRT.

3.2.5.4 Clinical implications

Whilst WB-MRI may have high specificity and negative predictive value, as discussed above, compared with standard of care tests to detect recurrent cancer post primary treatment, concordance between these imaging tests is low. Therefore, at present WB-MRI cannot be fully relied upon to detect radiorecurrent disease.

3.2.5.5 Future research

Larger studies with longer follow up is required before WB-MRI can fully replace bone scan and Choline PET/CT. One issue with these studies is metastatic disease and histopathological confirmation. There will have to be further ethical consideration as to whether bone biopsy can be incorporated and in which patients this will be feasible. Another issue is reporting bias as, clinicians should be blinded to the results of WB-MRI and not allow this to affect treatment plans as WB-MRI is yet to be validated. We have overcome this in our study as WB-MRI was not discussed at MDT outcomes and treatments were made in accordance to Choline PET/CT and bone scan as this is our current standard of care. Thus, longer follow up with a larger cohort of patients within the FORECAST study is likely to give an accurate outcome of the detection rates of WB-MRI and the concordance between this and standard of care tests. Overall this may add to growing evidence as to the clinical utility of WB-MRI and whether this can replace Choline PET/CT and bone scan in the diagnosis of radio-recurrent disease.

3.2.6 Conclusion

WB-MRI has similar detection rates of recurrent disease compared to bone scan and Choline PET/CT. However further studies are required to determine

if WB-MRI can replace these standard of care tests. Increased sample size as FORECAST completes recruitment and repeat WB-MRI imaging during follow up will determine the accuracy of WB-MRI to determine radiorecurrent disease thereby stratifying those patients amenable to further salvage therapy.

Chapter 4 Diagnosis of localised radiorecurrent prostate cancer

In this section the role of mpMRI, mpMRI targeted biopsies (MRI-TB) and template mapping biopsies (TPM) in the diagnosis of local radiorecurrent prostate cancer will be discussed. The first study is a retrospective analysis of men undergoing cognitive mpMRI-TB and TPM. The second study is a prospective study analysing the outcomes of mpMRI in the FORECAST Study in the detection of radiorecurrent disease. In the third study the outcomes of template mapping biopsy and implications for focal salvage therapy will be discussed.

4.1 Targeted transperineal prostate biopsy in the detection of radiorecurrent prostate cancer

4.1.1 Introduction

For local salvage therapy to be delivered appropriately, an accurate determination of the presence or absence of localised recurrence is important. Although transrectal ultrasound (TRUS) systematic 10-12 core (87) guided biopsies can be used to detect or rule out local disease, they have inherent inaccuracies as a diagnostic strategy and may lead to inappropriate therapeutic decisions. As discussed above in section 1.5 TRUS-guided biopsies can miss clinically significant disease, can misclassify significant disease as insignificant and may detect small volume clinically insignificant disease that may inappropriately be attributed as the cause of biochemical failure, when actually micro-metastatic disease may be the cause of a rising prostate-specific antigen (PSA) (88,89). These errors may lead to a patient undergoing improper management such as being started on ADT rather than potentially curative local therapy or unnecessary local salvage therapy with the presumption that metastases are not present.

Transperineal Template Mapping biopsies (TPM) overcomes these errors as

biopsy cores are taken every 5-10 mm. This is a highly accurate technique as the prostate gland is thoroughly sampled with co-ordinates to guide the process and recorded to correlate with any suspicious areas in the prostate as identified by MRI. Indeed in a treatment-naive prostate gland, when compared with current standard TRUS biopsy, 5mm TPM has been shown to be a more accurate diagnostic method (39,40).

Multi-parametric magnetic resonance imaging (mpMRI) using T2weighted, dynamic contrast enhanced (DCE-MRI) and diffusion weighted imaging (DWI), has gained much interest in the diagnosis of prostate cancer in the primary setting (90,91). A limited number of studies have shown that mpMRI may have encouragingly high performance characteristics in the radio-recurrent setting (43,44,92-94).

In this study cancer detection rates of biopsies targeted to an mpMRI-detected lesion (MRI-targeted biopsy: MRI-TB) was compared against TPM in men with rising PSA after prior radiotherapy. The use of TPM in this setting allowed us to compare the performance of targeted biopsies in all men who underwent mpMRI due to biochemical failure without selection bias. This study is START and STARD compliant (95).

4.1.2 Methods and Materials

Research ethics committee exemption was granted for this study by the institutional research office. A retrospective analysis identified 147 consecutive men, between July 2006 and May 2014, referred with suspicion of radio-recurrent prostate cancer due to rising PSA post-external beam radiotherapy (EBRT) or brachytherapy, a lesion suspicious for cancer on mpMRI and who subsequently underwent TPM biopsies. We contacted all referring physicians and sent reminders to collate all pre-radiotherapy baseline disease characteristics. All men had no evidence of distant disease based on a combination of radioisotope bone scan and computed tomography/positron emission tomography scans (FDG initially and later 18F-

choline). This is the standard of care for such patients referred to our institution for consideration of local salvage therapy. 70 men were excluded as they did not have MRI-TB. Therefore our cohort comprised 77 men who underwent an MRI-TB at the same time as TPM biopsies. MRI-TB was taken first, followed by TPM. Eight men were referred having been started on ADT and underwent imaging while on hormones. Eleven men underwent biopsy while on hormonal treatment, which had been started post-imaging in three. The mean time for hormonal treatment in these eleven was 8 months. Complications were assessed on review of subsequent clinic appointments.

4.1.3 Magnetic Resonance Imaging

The MRI scans were prospectively reported (blind to all histology). Reports were conducted by several expert uro-radiologists. Radiologists had access to all baseline clinical data, including pre-radiotherapy disease characteristics and post-radiotherapy PSA kinetics, where available. Due to the nature of the aims of our study (to determine the clinical validity of MRI targeting) there was no need for double reporting, as the targeting was based on the report issued at the time. Each prostate was divided into four sectors in three sections (base, mid-gland, apex) with the urethra as the anatomical dividing point between right and left and anterior and posterior. Each of the 12 resulting sectors and seminal vesicles were scored using the five-point Likert scale (1, highly likely no tumour; 5, highly likely tumour) (96).

As this is a retrospective study, from the period 2007-2014 scans were reported before the European Consensus report on prostate MRI and the ESUR guidelines on reporting of prostate MRI (96,97). However, our three senior uro-radiologists were formally involved in both guidelines and much of how we reported the scans in this series is currently incorporated into the ESUR and British Society of Uro-Radiology guidelines (98).

Patients were scanned on the 1.5T scanner (Symphony or Avanto, Siemens AG, Munich, Germany) using a pelvic phased-array coil. The sequences were

evaluated in the following manner. First, the T2 sequences were used to provide morphology and anatomical localisation. DCE played a greater role for the peripheral zone with the additional reference of the DWI scans. A score of 1 or 2 was given if there was no enhancement; a score of 3 was given if symmetrical diffuse enhancement was seen; if there was focal or asymmetrical enhancement 3 mm and no abnormality seen on DWI, a score of 4 was given; if there was focal or asymmetrical enhancement 3 mm and/or corresponding DWI abnormality in the same anatomical location, a score of 5 was recorded. A similar technique was used to report for lesions in the transition zone, with DWI sequences given greater weighting compared with DCE. DCE shows more enhancement of adenomas in this zone, especially after radiotherapy. However, an equivocal score of 3 based on DWI could be upgraded to 4 or 5 if there was an associated obvious DCE abnormality in the same anatomical location (44).

4.1.4 Transperineal prostate mapping biopsy

A 5 mm transperineal brachytherapy grid was used to take biopsies transperineally under general anaesthetic using TRUS guidance. Individual lesions that scored 3-5 were first targeted using the template grid with two to four cores taken per target. This was followed by TPM biopsies from the remainder of the prostate, which included the targeted biopsy area. If the prostate apex-base length was greater than the core length, two biopsies were taken at the same grid coordinate and labelled separately. Biopsies were taken in 20 sectors with one to two cores per sector according to the size of the prostate (Figure 1 - Transperineal Prostate Mapping Modified Barzell Zones) (39).

Biopsy cores were analysed and reported by two dedicated expert uro-pathologists with over 10 years of experience in the diagnosis of prostate malignancy. Biopsy results were grouped into four regions of interest per prostate, reflecting the mpMRI reporting. Pathologists were aware of clinical details and MRI findings.

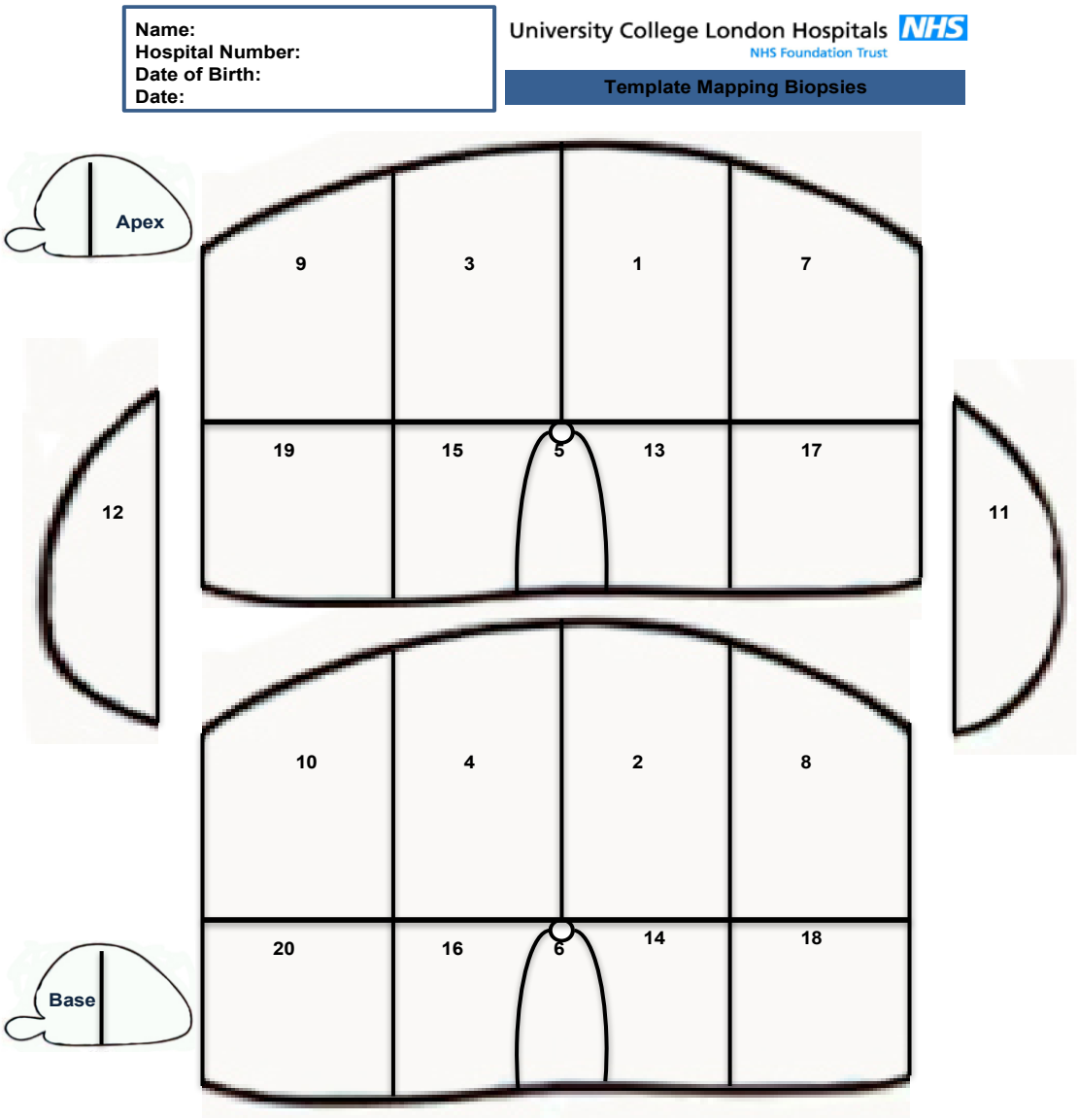
Statistical Analysis

The analysis was carried out at the whole prostate level. Two-by-two and three-by-three tables of agreement were drawn up comparing the detection of clinically significant, clinically insignificant and no cancer by each of the two-biopsy techniques.

The primary outcome was the detection rate of clinically significant prostate cancer (defined using UCL/Ahmed definition 2 (Gleason ≥3+4 and/or maximum cancer core length (MCCL) ≥4 mm) (99).

Secondary outcomes were set for a target definition of UCL/ Ahmed definition 1 cancer only (Gleason ≥4+3 and/or MCCL ≥ 6 mm only), excluding those that met criteria of UCL/ Ahmed definition 2), any Gleason pattern 4 or greater and 'all cancer'. The UCL definitions were used as they were developed specifically and validated for the presence of 0.2 cm3 and 0.5 cm3 lesions on a TPM sampling strategy (99). For each target condition, the difference between the biopsy techniques was compared using McNemar's test. Data were analysed using SPSS version 22 (IBM Corp 1989, 2013 Release 22.0.0.0). A P value < 0.05 was chosen for indicating a statistically significant difference.

Figure 1 – Transperineal Prostate Mapping Modified Barzell Zones



Modified Barzell Zones

1 Left Parasagital Anterior Apex
2 Left Parasagital Anterior Base
3 Right Parasagital Anterior Apex
4 Right Parasagital Anterior Base
5 Midline Apex
6 Midline Base
7 Left Medial Anterior Apex
8 Left Medial Anterior Base
9 Right Medial Anterior Apex
10 Right Medial Anterior Base
11 Left Lateral
12 Right Lateral
13 Left Parasagital Posterior Apex
14 Left Parasagital Posterior Base
15 Right Parasagital Posterior Apex
16 Right Parasagital Posterior Base
17 Left Medial Posterior Apex
18 Left Medial Posterior Base
19 Right Medial Posterior Apex
20 Right Medial Posterior Base

HGPIN / atypical acini

Clinically insignificant disease (G3+3 up to 3mm)

Gleason = 3+4 AND/OR Max Cancer length 4-5mm

Gleason >/= 4+3 AND/OR Max cancer length >/=6mm

4.1.5 Results

Of 77 patients included, the mean age was 70 years (range 61-82; standard deviation 5.03). The median PSA at the time of radiotherapy was 14 ng/ml (range 4.5-143; interquartile range 7.83-32.50). Information on pre-radiotherapy stage and risk was available for 63 patients. Further baseline information is available in Table 18. Adverse event data were available in all 77; one reported haematospermia (1.3%), three (3.9%) reported dysuria with no associated infection/sepsis and one (1.3%) had fever and bowel disturbance treated with oral antibiotics for presumed gastrointestinal infection.

Table 18 Baseline demographics of patients undergoing transperineal biopsies for suspicion of radio-recurrent prostate cancer

Baseline Demographics	
Total no. patients	77
Mean age (range) years (standard deviation)	70.48 (61-82) (5.03)
Median PSA (ng/ml at) EBRT (range) (IQR)	14 (4.5-143; IQR 7.83-32.5)
D'Amico risk score at time of EBRT, n (%)	
Risk information known	63 (100)
1 High risk: PSA > 20, G > 8, T2c - 3a	33 (52.4)
2 Intermediate risk: PSA ≥ 10 ≤ 20, G7, or T2b	19 (30.2)
Low risk: PSA < 10, G < 6, T1-T2a	11 (17.5)
Time between EBRT and biochemical failure (months), median (range) (IQR)	60 (5-156; IQR 36.75-85.00)

PSA at time of MRI (ng/ml), median (range) (IQR)	4.68 (0.54-20; IQR 2.68-7.60)
Time between EBRT and TPM (months), median (range) (IQR)	78 (15-199; IQR 61.5-110)
Time between mpMRI and TPM (months), median (IQR)	2.76 (1.58-4.34)

4.1.5.1 Primary Outcome

4.1.5.1.1 Detection of Clinically Significant Cancer

Using University College London (UCL)/Ahmed definition 2 (Gleason ≥3+4 and/or maximum cancer core length (MCCL) ≥4 mm), 60 patients (77.9%) on MRI-TB compared with 66 patients (85.7%) on TPM (Table 19) were identified. In terms of agreement, three (3.9%) classified as clinically insignificant or no cancer on TPM were found to have clinically significant cancer on MRI-TB. Nine (11.7%) reported as having no cancer or clinically insignificant cancer on MRI-TB were found to have clinically significant cancer on TPM (p=0.15) (Table 20). Eight of these cases were of cancer in the targeted area (targeting error) and one had cancer outside of the targeted area (mpMRI detection error). This patient had an overall mpMRI score of 3/5 in all areas of the prostate, the left posterior on TPM biopsy was found to be positive for Gleason 4+3 MCCL 1 mm. The posterior midline was targeted in this patient, but this did not reveal any cancer.

On a per core analysis, 190/381 (50%) of MRI-TB cores were positive for clinically significant cancer compared with 425/2392 (17.8%) of TPM cores (Table 4). For the detection of clinically significant prostate cancer, 2.0 MRI-TB cores had to be taken versus 5.6 cores on TPM biopsy (Table 21).

Table 19 Cancer detection rates using transperineal prostate mapping (TPM) and magnetic resonance imaging-targeted biopsies (MRI-TB) in patients with radio-recurrent prostate cancer

	TPM n (%)	**MRI-TB n (%)**
Total	77 (100)	77 (100)
No cancer	8 (10.4)	14 (18.2)
Clinical insignificant (Gleason 3+3 and ≤3 mm)	3 (3.9)	3 (3.9)
UCL/Ahmed definition 2 (Gleason ≥3+4 and/or maximum cancer core length (MCCL) ≥4 mm)	11 (14.3)	8 (10.4)
UCL/Ahmed definition 1 Gleason ≥4+3 and/or MCCL ≥ 6 mm	55 (71.4)	52 (67.5)

Table 20 Comparison of clinically significant cancer detection between transperineal prostate mapping (TPM) and magnetic resonance imaging-targeted biopsies (MRI-TB) cognitive, visual-estimation method in patients with radio-recurrent prostate cancer

			TPM	
		No cancer/clinically insignificant cancer	UCL/Ahmed definition 2 or UCL/Ahmed definition 1	Total
	No cancer/clinically insignificant cancer	8	9	17

MRI-TB	UCL/Ahmed definition 2 or UCL/Ahmed definition 1	3	57	60
	Total	11	66	77

Table 21 Core-based comparison of the detection of any cancer, clinically significant cancer and cancer Gleason 7 between transperineal prostate mapping (TPM) and magnetic resonance imaging-targeted biopsies (MRI-TB) cognitive, visual-estimation method in patients with radio-recurrent prostate cancer

	TPM (%)	**MRI-TB (%)**
Total number of cores	2392 (100)	380 (100)
Any cancer	428 (17.9)	203 (53.4)
UCL/Ahmed definition 2 or UCL/Ahmed definition 1	425 (17.8)	190 (50.0)
Gleason score ≥7	419 (17.5)	181 (47.6)
UCL/Ahmed definition 1	379 (15.8)	177 (46.6)

4.1.5.2 Secondary Outcomes

First, MRI-TB had a similar rate of detection of UCL/ Ahmed definition 1 disease compared with TPM; 52 patients (68%) versus 55 patients (71%). For the detection of clinically significant prostate cancer, 2.2 MRI-TB cores had to be taken versus 6.3 cores on TPM biopsy.

Second, TPM had a higher detection rate of Gleason 3+4 cancer compared with MRI-TB; 65 patients (84.4%) versus 58 patients (75.3%). For the detection of Gleason cancer ≥3+4, 2.1 MRI-TB cores had to be taken versus 6.3 cores on TPM biopsy.

Third, TPM had a higher all cancer detection rate of 69 patients (89.6%) compared with 63 patients (81.8%) for MRI-TB. TPM misclassified one patient (1.3%) as no cancer but was found to have cancer on MRI-TB. However, MRI-TB misclassified seven patients (9.1%) as no cancer but were found to have cancer on TPM biopsy. These cases were of cancer in the targeted area (targeting error) in seven cases (P = 0.07) (Table 22). Fourth, based on MRI score, 67/77 patients (87.0%) scored PIRADS ≥4 (Table 23), of which 60/67 patients (90.0%) were found to have clinically significant cancer on TPM and 57/67 patients (85.1%) on MRI-TB (Table 24). Ten of 77 had an mpMRI score of ≤ 3/5. Of these, 6/10 (60%) had clinically significant cancer on TPM (all had Gleason score ≥ 7). On MRI-TB, 3/10 (30%) had clinically significant cancer (with two of these having Gleason score ≥ 7).

Table 22 Comparison of cancer detection between transperineal prostate mapping (TPM) and magnetic resonance imaging-targeted biopsies (MRI-TB) cognitive, visual-estimation method in patients with radio-recurrent prostate cancer

			TPM	
		No cancer	Any cancer	Total
	No cancer	7	7	14
MRI-TB	Any cancer	1	62	63
	Total	8	69	77

Table 23 Magnetic resonance imaging (MRI) score and detection of any cancer, clinically significant cancer and Gleason ≥7 by transperineal prostate mapping in patients with radio-recurrent prostate cancer

MRI score	n (%)	Any cancer n (%)	UCL/Ahmed definition 2 or UCL/Ahmed definition 1 n (%)	Gleason ≥7 n (%)	UCL/Ahmed definition 1 n (%)
1. Clinically significant disease is highly unlikely to be present	0	0	0	0	0
2. Clinically significant cancer is unlikely to be present	1	0	0	0	0
3. Clinically significant cancer is equivocal	9	6	6	6	2
4. Clinically significant	25	22	20	19	17

cancer is likely to be present					
5. Clinically significant cancer is highly likely to be present	42	41	40	40	36
Total	77	69	66	65	55

Table 24 Magnetic resonance imaging (MRI) score and detection of any cancer, clinically significant cancer and Gleason 7 by MRI-targeted biopsies cognitive, visual-estimation method in patients with radio-recurrent prostate cancer

MRI score	**n (%)**	**Any cancer n (%)**	**UCL/Ahmed definition 2 or UCL/Ahmed definition 1 n (%)**	**Gleason ≥7 n (%)**	**UCL/Ahmed definition 1 n (%)**
1. Clinically significant disease is highly unlikely to be present	0	0	0	0	0

2. Clinically significant cancer is unlikely to be present	1	0	0	0	0
3. Clinically significant cancer is equivocal	9	3	3	2	2
4. Clinically significant cancer is likely to be present	25	21	19	19	17
5. Clinically significant cancer is highly likely to be present	42	39	38	37	33
Total	77	63	60	58	52

4.1.6 Discussion

4.1.6.1 Summary of Results

MRI-TB detected 77.9% of patients with clinically significant cancer (UCL/Ahmed Definition 2 disease), whereas TPM biopsy had an 85.7% detection rate (p=0.146). On a per core analysis, 190/381 (50%) of MRI-TB cores were positive for clinically significant cancer compared with 425/2392 (17.8%) of TPM cores (Table 4). For the detection of clinically significant prostate cancer, 2.0 MRI-TB cores had to be taken versus 5.6 cores on TPM biopsy (Table 4).

First, MRI-TB had a similar rate of detection of UCL/ Ahmed definition 1 disease compared with TPM (52 patients (68%) versus 55 patients (71%) (P=0.629)). However, TPM biopsy had a higher detection rate of Gleason 3+4 and all cancer detection rate compared with MRI-TB ((65 patients (84.4%) versus 58 patients (75.3%) (p=0.092) and 69 (89.6%) compared with 63 patients (81.8%) (p=0.70).

4.1.6.2 Limitations

Before discussing the clinical implications of our findings, our study does have some limitations. First, the retrospective design and small sample size limits the external validity of our findings. Second, as nearly all of our patients were referred from external centres, there was incomplete information on radiotherapy doses, initial PSA and initial Gleason scores. Third, although the notion of clinically important disease is gaining acceptance in primary prostate cancer, such a notion has not been adequately explored in radiorecurrent disease. To mitigate this, we evaluated outcomes using a number of histological target definitions. It has been reported that delayed tumour regression and eventual conversion to negative biopsies occurs at a mean time of 30 months (100) [20]. However, within our study, only one patient was sampled within 30 months (at 15 months) of completion of radiotherapy. The average time after EBRT for biopsy was 86 months. Thus, any cancer

detected will probably be a true recurrence and not a continuing change in prostate tissue morphology from radiation.

4.1.6.3 Comparison with Existing Studies

Sensitivity and specificity of mpMRI have been reported as high as 86-100% (43,94,101). However, these studies used TRUS biopsy as the reference standard, so the mpMRI detection error may have been under-reported. There are limited data available about the use of targeted biopsy in the radio-recurrent setting. Rud et al. (102) examined the detection rate of DWI and MRI-US fusion-targeted biopsy (MRI-US fusion-TB) in men with radio-recurrent prostate cancer. MRI-US fusion-TB had a higher rate of detection of cancer compared with random TRUS-guided biopsies - 83% versus 21%, respectively. However, a poor reference standard was used in this study and random biopsies were not carried out in the area where a targeted biopsy had been undertaken. Instead random TRUS-guided biopsies were taken in the contralateral lobe.

In order to further place our data in the context of targeted biopsy series, we have to turn to the primary setting. There are several studies that report on the improved detection of cognitive MRI-TB and now MRI-US fusion-TB compared with whole-gland sampling in the primary setting. One study showed similar detection rates of MRI-TB versus TPM in primary prostate cancer of 57% versus 62% (P = 0.174). This study also showed a higher proportion of cores positive for cancer with MRI-TB (38%) than with TPM (14%) (42). MR-US fusion biopsies have reported higher cancer detection rates compared with standard sampling. One study compared MRI-US fusion-TB with transperineal biopsy in the primary setting and found that 46.0% of MRI-US fusion-TB versus 7.5% of systematic TPM detected Gleason ≥7 cancers. TPM biopsy missed 20.9% Gleason ≥7 cancers compared with 12.8% for MRI-US fusion-TB (103).

A more recent study also showed that MRI-US fusion-TB resulted in 22% and 67% additional cases of Gleason ≥3+4 and Gleason ≥4+3 prostate cancer than 12 core systematic biopsy, respectively (104).

Two recent systematic reviews have shown MRI-TB to be superior when compared with whole-gland transrectal systematic sampling. Moore et al. (105) examined MRI-TB compared with whole-gland sampling in the primary setting. Core-based analysis showed that just 7% of systematic cores were positive for any cancer compared with 30% on MRI-TB. On a per patient basis, MRI-TB had a higher cancer detection rate of 48% versus 36% for standard biopsy. Both targeted and standard biopsy detected clinically significant cancer in 43% with similar rates of missing cancer (23.4% versus 21.6%, respectively).

Another systematic review (106) reported on cancer detection rates of MRI-US fusion-TB in comparison with systematic biopsy. Clinically significant cancer was detected in 33.3% versus 23.6%, respectively. MRI-US fusion biopsy was again re-ported to be more efficient, with four times the number of cores needed in systematic sampling compared with an MR-US fusion-TB approach. MRI-US fusion biopsies also detected a median of 9.1% additional clinically significant cancers that were missed by standard biopsy alone. Conversely, standard biopsies detected a median of 2.1% additional clinically significant cancers that were missed by MRI-US fusion-TB.

It is important to note that these systematic reviews predominantly examined targeted biopsy in the primary setting. If our results are reproducible in further studies and larger numbers across multiple sites, it is possible that in future, men who fail radiation therapy and who wish to consider local salvage therapy should undergo an mpMRI with targeted biopsies to suspicious areas to confirm histological local recurrence. As with all diagnostic tests and strategies, a balance between accuracy and burden of the test(s) needs to be evaluated. The additional number of biopsy cores that are taken from TPM do lead to a 10% higher detection rate, but in themselves are not perfect either as misclassification does occur. Patients and their physicians need to make

an individualised decision, weighing up the additional detection rate with the requirement for TPM to be carried out under general anaesthetic with a high number of cores and the side-effects that these cause. Future research needs to focus on whether image-fusion targeting has any clinical utility in this setting or whether mpMRI cognitive, visually directed biopsies, as we have carried out in our study, is sufficient. Furthermore, mpMRI with targeted biopsy confirmation may facilitate greater acceptance or delivery of local salvage therapies, such as radical prostatectomy, or minimally invasive approaches, such as tissue-preserving focal salvage therapy (107).

4.1.6.4 Clinical Implications

To our knowledge, this is the first study to compare cancer detection rates of MRI-TB and TPM biopsies in the radio-recurrent prostate cancer setting. We found that MRI-TB has an encouraging and acceptable detection rate for clinically significant prostate cancer using any number of definitions (68.0-77.9%). Although TPM biopsies had 10% higher detection rates for a more conservative definition of clinically significant cancer, the performance was similar for a higher threshold of disease burden. MRI-TB was also consistently more efficient, with fewer biopsies required compared with TPM; 1 core versus 2.8 cores for the detection of clinically significant disease; 1.00 core versus 2.9 cores for UCL/Ahmed definition 1 disease, respectively. MRI-TB misclassified seven patients (9.1%) as no cancer but were found to have cancer on TPM biopsy. These cases were of cancer in the targeted area (targeting error) in seven cases (P = 0.07).

4.1.6.5 Future Research

To further improve the targeting accuracy of MRI-TB US-Fusion and live MRI-TB holds promise. At time of biopsy, patient position (lithotomy) and presence of a transrectal probe can alter the shape of the gland resulting in differences of target sites identified on pre-operative MRI. These newer fusion techniques can be compared to cognitive and TPM biopsy, eventually providing more

evidence as to the best strategy to identify local radiorecurrent disease that causes least morbidity to the patient.

4.1.7 Conclusions

MRI-TB show some promise in the diagnosis of clinically significant radio-recurrent prostate cancer when compared with a systematic biopsy approach using TPM biopsies. Further prospective multicentre trials are needed to determine if these results are stable and reliable across a larger number of men.

4.2 Multiparametric MRI in detection of radiorecurrent disease

4.2.1 Introduction

Accurate localization of radiorecurrent disease is paramount in providing focal salvage therapy. Multi-parametric MRI (MpMRI) has been shown to have promise in the diagnosis of radiorecurrent disease as discussed above. The detection rate of mpMRI within the FORECAST Study will now be discussed and the detection rates of TPM biopsy versus MRI-TB.

4.2.2 Methods and Materials

Patient selection

Eligibility criteria for the trial primarily include men who biochemical failure after having had previous external beam radiotherapy or brachytherapy with or without neo-adjuvant/adjuvant hormone therapy. Biochemical failure as defined by the Phoenix criteria (PSA nadir + 2 ng/ml).

See Appendix 10.1 for protocol with full inclusion and exclusion criteria.

Imaging

All patients underwent Choline PET/CT, radio-isotope bone-scan (if not already carried out in the last 6 months and whole-body MRI (See above Flowchart 1 – FORECAST Study). If these investigations revealed metastatic disease they were withdrawn from the trial.

Multi-parametric Resonance Imaging (mpMRI)

As discussed above in Chapter 4.1 - Targeted transperineal prostate biopsy in the detection of radiorecurrent prostate cancer patients were scanned on the 1.5T scanner (Symphony or Avanto, Siemens AG, Munich, Germany) using a pelvic phased-array coil. The MRI scans were prospectively reported (blind to all histology). Reports were conducted by several expert uro-radiologists.

Radiologists had access to all baseline clinical data, including pre-radiotherapy disease characteristics and post-radiotherapy PSA kinetics, where available.

As discussed above in Chapter 4.1 each prostate was divided into four sectors in three sections (base, mid-gland, apex) with the urethra as the anatomical dividing point between right and left and anterior and posterior. Each of the resulting sectors and seminal vesicles were scored using the five-point MRI and the ESUR guidelines on reporting of prostate MRI (96,97) 1, highly likely no tumour through to 5, highly likely tumour.

Biopsy Strategies

Patients then underwent transperineal prostate mapping biopsy (as described above (see Chapter 4.1 Targeted transperineal prostate biopsy in the detection of radiorecurrent prostate cancer) using a modified version of that described by Barzell et al. (74) (See Figure 1 - Transperineal Prostate Mapping Modified Barzell Zones above- Chapter 4.1 Targeted transperineal prostate biopsy in the detection of radiorecurrent prostate cancer).

If mpMRI prior to biopsy identified a visible lesion, MRI cognitive targeted sampling were taken by comparing the pre-intervention mpMRI to the live intra-operative prostate ultrasound on two different screens (cognitive or visually targeted). TPM biopsies were performed as described above using a 5 mm brachytherapy template grid with two to four cores taken per target. This was followed by TPM biopsies from the remainder of the prostate, which included the targeted biopsy area. (39,44).

Biopsy cores were analysed and reported by two dedicated expert uro-pathologists with over 10 years of experience in the diagnosis of prostate malignancy. Biopsy results were grouped into four regions of interest per prostate, reflecting the mpMRI reporting. Pathologists were aware of clinical details and MRI findings.

Statistical Analysis

The analysis was carried out at the whole prostate level. Two-by-two tables of agreement were drawn up comparing the detection of any cancer, clinically significant UCL Definition 1 and Clinically significant cancer UCL Definition 2 disease. To calculate the sensitivity and specificity, scores of PIRADS ≥ 4 were considered positive and further analysis of scores PIRADS ≥ 3 as positive. The primary outcome was the detection rate of clinically significant prostate cancer (defined using UCL/Ahmed definition 2 (Gleason ≥3+4 and/or maximum cancer core length (MCCL) ≥4 mm) (99). Secondary outcomes were set for a target definition of UCL/ Ahmed definition 1 cancer only (Gleason ≥4+3 and/or MCCL ≥ 6 mm only), excluding those that met criteria of UCL/ Ahmed definition 2), and any cancer. The UCL definitions were used as they were developed specifically and validated for the presence of 0.2 cm3 and 0.5 cm3 lesions on a TPM sampling strategy (99).

Data were analysed using SPSS version 24 (IBM Corp 1989, 2013 Release 22.0.0.0). A P value < 0.05 was chosen for indicating a statistically significant difference.

4.2.2.1 Results

Of 36 patients included, the mean age was 69 years (range 54-85; standard deviation 7.09). The median PSA at the time of radiotherapy was 14.8 ng/ml (range 3.6-358; interquartile range 7.32-32.35). Information on pre-radiotherapy stage and risk was available for 34 patients. 8.8% (3/34), 29.4% (10/34) and 61.8% (21/34) were low, intermediate risk and high risk D'Amico Score at baseline prior to radiotherapy respectively.

4.2.2.1.1 Primary Outcome

For detection of clinically significant cancer as defined by UCL Definition 2 (Gleason =3+4 OR any grade of cancer length 4-5mm) using PIRADS ≥ 4,

Sensitivity, specificity, PPV and NPV was 90%, 81.3%, 85.7% and 86.7% respectively. Area under ROC Curve (AUROC) was 0.856 (SE 0.07 p=0.000) (See Table 25 and Figure 3 below).

Table 25 – Detection of Clinically significant cancer using UCL 2 Definition – MRI PIRADS ≥4 as positive

		UCL Definition 2 TPM		
MRI PIRADS ≥4		No	Yes	Total
	No	13	2	15
	Yes	3	18	21
	Total	16	20	36

Table 26 - Detection of Clinically significant cancer using UCL 1 Definition – MRI PIRADS ≥4 as positive

		UCL Definition 1 TPM		
MRI Any cancer PIRADS ≥4		No	Yes	Total
	No	13	2	15
	Yes	4	17	21
	Total	17	19	36

Table 27 - Detection of any cancer– MRI PIRADS ≥4 as positive

		Any cancer on TPM		
MRI Any cancer		No	Yes	Total
	No	12	3	15
	Yes	3	18	21

PIRADS ≥4	Total	15	21	36

Figure 3 UCL Def 2 on TPM - MRI Score PIRADS ≥4

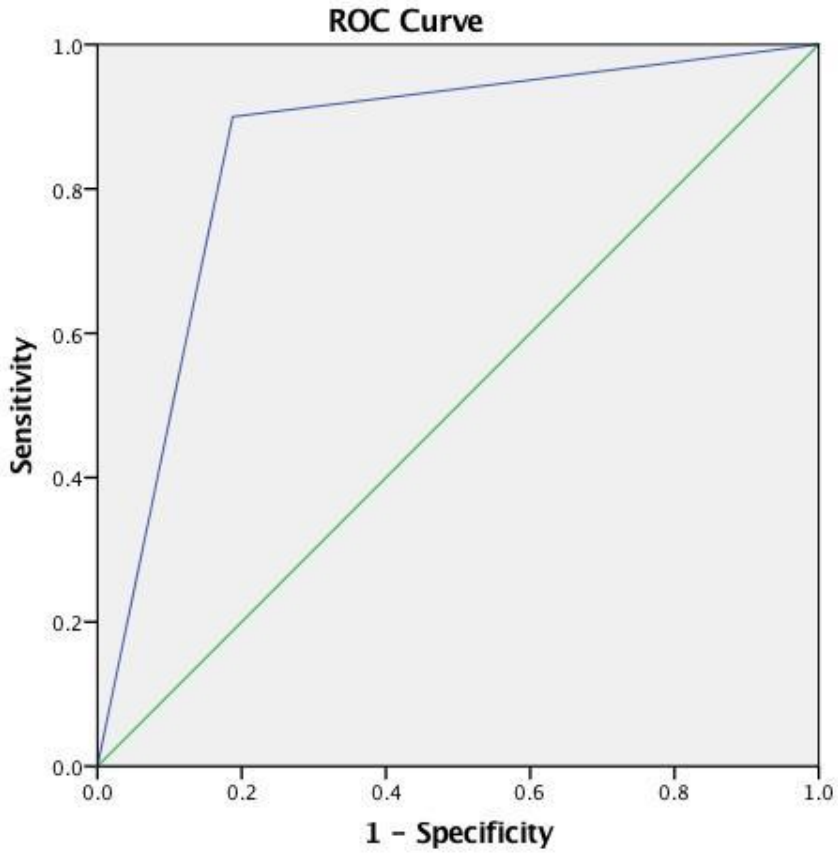
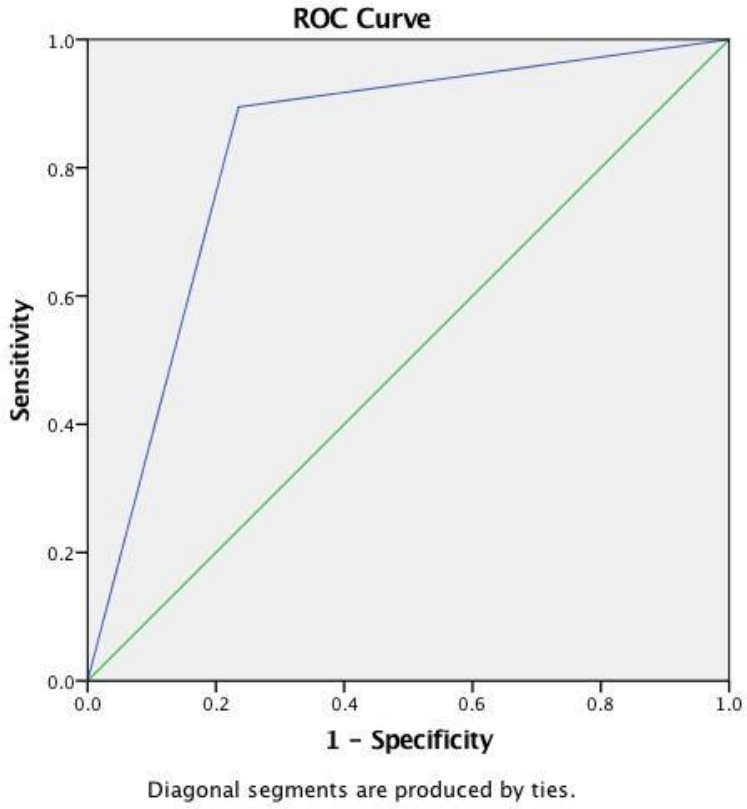


Figure 4 - UCL Def 1 on TPM - MRI Score PIRADS ≥4



For detection of clinically significant cancer as defined by UCL Definition 1 (Gleason >/=4+3 OR any grade of cancer length >/=6mm) PIRADS ≥ 4 had a sensitivity, specificity, PPV and NPV was 89.5%, 76.5%, 81% and 86.8% AUROC was 0.83 (SE 0.074 p=0.001) (See Table 26 and Figure 4). Sensitivity, specificity, PPV and NPV of MRI score ≥4 for detection of any cancer was 85.7%, 80%, 85.7% and 80% respectively (p=0.00), (AUROC) was 0.829 (SE 0.075 p=0.01) (See Table 27 and Figure 5).

Figure 5 - Any cancer on TPM - MRI Score PIRADS ≥4

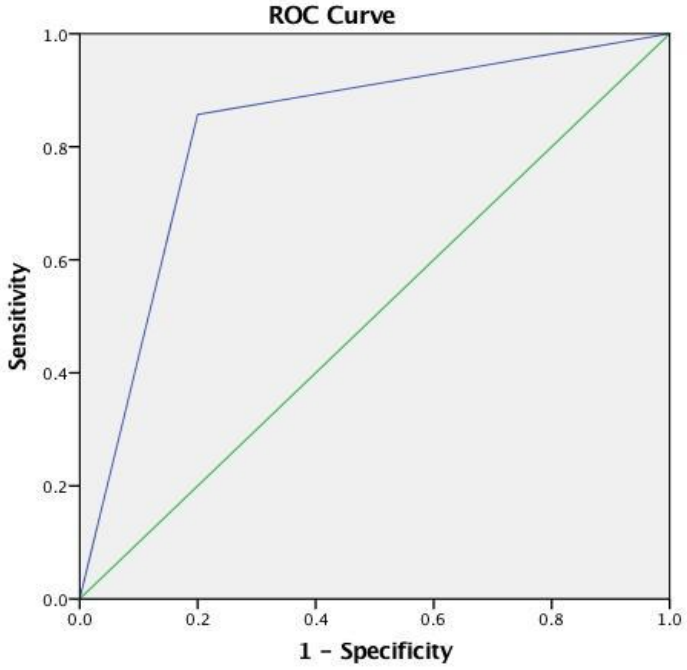


Table 28 – Detection of Clinically significant cancer using UCL 2 Definition – MRI PIRADS ≥4 as positive

		UCL Definition 2 TPM		
		No	Yes	Total
MRI Any cancer PIRADS ≥3	No	12	2	14
	Yes	3	14	17
	Total	15	16	31

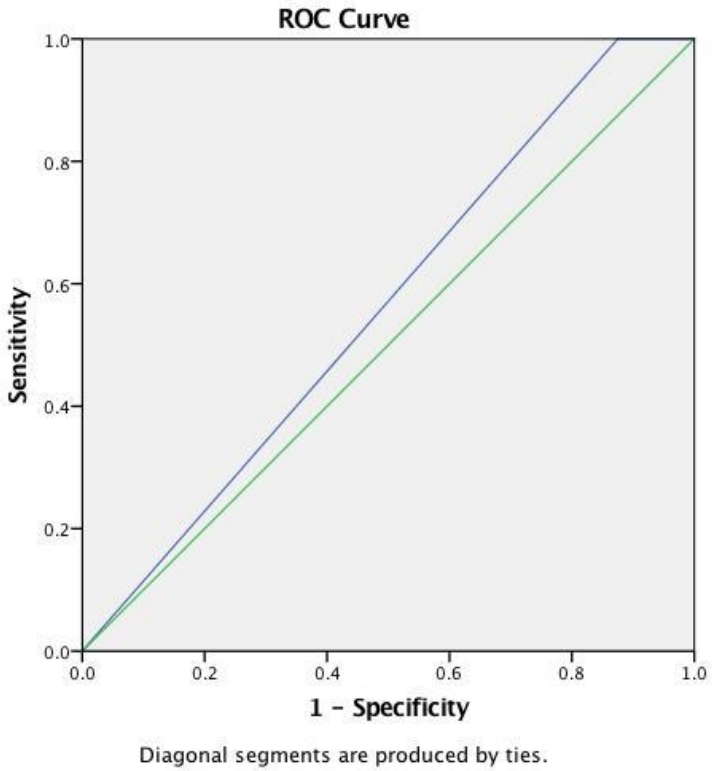
Table 29 - Detection of Clinically significant cancer using UCL 1 Definition – MRI PIRADS ≥4 as positive

		UCL Definition 1 TPM		
		No	Yes	Total
MRI Any cancer PIRADS ≥3	No	12	2	14
	Yes	4	13	17
	Total	16	15	31

Table 30 - Detection of any cancer– MRI PIRADS ≥4 as positive

		Any cancer on TPM		
		No	Yes	Total
MRI Any cancer PIRADS ≥3	No	11	3	14
	Yes	3	14	17
	Total	14	17	31

Figure 6 - UCL Def 2 on TPM - MRI Score PIRADS ≥3



Using MRI Score >3 for detection of clinically significant cancer as defined by UCL Definition 2 Sensitivity, specificity, PPV and NPV was 87.5%, 80.0%, 82.4% and 85.7% respectively and AUROC was 0.563 (SE 0.1 p=0.52). Sensitivity, specificity, PPV and NPV to detect clinically significant cancer as defined by UCL Definition 1 was 86.7%, 75.0%, 76.5% and 85.7% (AUROC) was 0.559 (SE 0.098 p=0.55). Sensitivity, specificity, PPV and NPV of MRI to detect any cancer was 82.4%, 78.6%, 82.4% and 78.6% AUROC was 0.567 (SE 0.1 p=0.5) (See tables 28-30 and Figure 6).

Table 31 – TPM Vs. MRI-TB Core based analysis

	TPM	**MRI-TB**
Total Cores n (%)	1254 (100)	150 (100)
Any cancer cores n (%)	149 (11.9)	54 (36)
UCL Def 1 Cores n (%)	128 (10.2)	50 (33.3)
UCL Def 2 Cores n (%)	134 (10.7)	70 (46.7)

1254 cores taken using TPM biopsy of which 149 cores (11.9%) were positive. 150 targeted biopsies (up to 3 areas being targeted) were taken, of which 54 were positive (36%) (See Table 31).

Table 32 – MRI-TB vs. TPM in detection of clinically significant cancer UCL Definition 2

Detection of UCL Definition 2 Cancer				
		TPM		
MRI-TB		No	Yes	Total
	No	16	6	22
	Yes	0	14	14
	Total	16	20	36

When comparing the detection rate of TPM vs. MRI-TB in the detection of clinically significant disease as defined by UCL –Definition 2, TPM and MRI-TB were concordant in 14 cases as being positive, 16 cases as negative and no cases on TPM misclassifying disease. Whereas there were 6 cases

misclassified on MRI-TB as negative for clinically significant cancer, that were found to be positive on TPM (See Table 32).

Table 33 – MRI-TB vs. TPM in detection of clinically significant cancer UCL Definition 1

UCL Definition 1				
		TPM		
MRI-TB		No	Yes	Total
	No	17	5	22
	Yes	0	14	14
	Total	17	19	36

Both MRI-TB and TPM detected clinically significant cancer as defined by UCL Definition 1 disease in 14 cases and was negative in 17 cases. TPM did not misclassify any patients however MRI-TB reported 5 cases to be negative for UCL Definition 1 disease that was positive on TPM biopsy (See Table 33)

Table 34 – MRI-TB vs. TPM in detection of any cancer

Any cancer				
		TPM		
MRI-TB		No	Yes	Total
	No	15	7	22
	Yes	0	14	14
	Total	15	21	36

In the detection of any cancer, both techniques were concordant in 29 cases, (14 positive for cancer and 15 negative for cancer). 7 cases on MRI-TB were classified as negative that were positive on TPM, no cases were misclassified by TPM. (See Table 34)

4.2.3 Discussion

4.2.3.1 Summary of results

MRI PIRADS 3 & 4 had a high Sensitivity, specificity, PPV and NPV for the detection of clinically significant cancer (UCL definition 2) of 87.5%, 80.0%, 82.4% and 85.7% respectively and 90%, 81.3%, 85.7% and 86.7% respectively.

TPM biopsy and MRI-TB were concordant in the majority of cases for detection of clinically significant cancer for both UCL Definition 1 & 2 disease, however, MRI-TB misclassified up to 6 patients as having no cancer, when clinically significant cancer was present on TPM biopsy.

4.2.3.2 Methodological limitations

Our study does have some limitations. The small sample size does limit the external validity of our findings. Clinically significant radiorecurrent cancer is yet to be defined and so a number of different definitions as used in primary prostate cancer diagnosis were evaluated. The average time after EBRT for biopsy was 78 months. Within our study only 2 patients were sampled within 30 months of finishing EBRT. Thus, any cancer detected is likely due to a true recurrence and not a continuing change in prostate tissue morphology from radiation which can occur if sampling occurs within 30 months (100).

Several studies (43,92,94,108) report on the utility of DCE as part of mpMRI in imaging radiorecurrent prostate cancer as after EBRT, it is difficult to distinguish between recurrence and treated prostate tissue which has low signal intensity with indistinct zonal anatomy on T2W. A limitation of this study is that individual mpMRI sequences were not explored to determine any increase in detection rates.

4.2.3.3 Comparison with Existing Studies

A meta-analysis performed by Wu et al. (109) found that mpMRI had a pooled sensitivity and specificity of 82% (95% CI 75-88%) and 74% (95% CI 64-82%), respectively with AUROC of 0.87 in the detection of recurrent cancer after radical treatment. Therefore, our study has also shown similar detection rates. Our study is also likely to be more accurate as previous studies examining the detection rate of mpMRI use TRUS biopsy (43,94,101) as reference standard which has high rates of under sampling. Some studies use salvage radical prostatectomy as reference standard. Pucar et al. (64) explored the role of MRI and MR spectroscopy in the detection of radiorecurrent cancer compared to DRE and TRUS biopsy. Whilst MRI and MRSI had higher sensitivity 68% and 77% respectively than TRUS and DRE, specificity of MRI was similar 96% vs. 95% and 96% respectively. MRSI had a specificity 78% vs. 95% and 96% compared to TRUS and DRE. However, the importance of this study is that sites of recurrence were the same pre-EBRT and post-EBRT and were clinically significant foci of cancer. Only 2 small insignificant cancer foci (small volume) were found that were not detected on post EBRT MRI.

Overall whilst MRI-TB may be more efficient in detecting radiorecurrent cancer, there are still misclassifications that occur similar to our previous reported study (Chapter 4.1 Targeted transperineal prostate biopsy in the detection of radiorecurrent prostate cancer). This can be due to several reasons; patient positioning at time of biopsy may not allow for access to target MRI lesions. Lesions seen on MRI may not be visible on US and therefore difficult to localise. The key to improving efficiency and accuracy of biopsy is to find a technique that aids accurate disease localization, MRI-US fusion may be an option as there may be less misregistration (110).

Yakar et al. examined MRI-Guided TRUS biopsy (MRI-GB) in the detection of radiorecurrent prostate cancer in 20 patients. 38 lesions were identified on pre-biopsy MRI. PPV of MRI-GB was found to be 78% in all patients and 68% in each of the tumour suspicious regions. This study does not report whether

there were further TRUS biopsies performed at the time of MRI-GB and so there is no comparison between guided and TRUS biopsies in the detection of cancer.

Menard et al. (111) examined MRI-guided transperineal prostate biopsy versus transperineal prostate biopsy – six cores were taken using each technique. Diagnostic accuracy of mpMRI was up to 0.82. However again within this study a direct comparison of MRI-GB versus systematic biopsies was not performed. 82% of patients within this study had unifocal recurrent disease which suggests patients presenting with radiorecurrent prostate cancer may be suitable to focal salvage therapy only as opposed to whole gland salvage therapy. This study however found that MRI was not sufficient to delineate tumour boundaries for focal salvage treatment.

Our study is one of the few studies that examines detection of clinically significant disease using an accurate reference standard. Compared with a recent systematic review (105) which compared MRI-TB to whole gland sampling in the primary based setting, our MRI-TB and systemic sampling had a higher detection rate of cancer 36% vs. 20% and 11.9% vs. 7% respectively. However, within this current study, there was a lower rate of clinically significant cancer UCL Definition 1 but a higher rate of UCL definition 2 cancer compared to systematic review, 50 vs. 43% and 70 vs. 43% respectively. It must be noted that there was not a single definition of clinically significant cancer within the systematic review as this varied according to each study included in the review.

4.2.3.4 Clinical implications

Our study has shown that mpMRI does have a role in the detection of radiorecurrent disease. PIRADS ≥4 has high detection rates of radiorecurrent cancer. MpMRI Score 3 however has a poor detection rate of clinically significant radiorecurrent cancers and therefore, lesions scoring PIRADS 3 should be biopsied.

4.2.3.5 Future research

Larger studies are required to further validate our findings. Each parameter of mpMRI – DWI, DCE, should be examined and compared to TPM biopsy to determine which has the highest detection rate of clinically significant radiorecurrent cancer. A definition for clinically significant radiorecurrent cancer should also be examined to see if these patients progress in a similar manner to primary cancer patients. Overall, further imaging and histopathological findings in radio-recurrent disease should be examined to reach a consensus on the most appropriate time, imaging and biopsy technique to accurately identify radiorecurrent disease. Currently the large majority of work is based in the primary cancer setting. It is important to achieve the same guidelines in the radiorecurrent setting to identify those men in need of and who may benefit the most from salvage treatment.

4.2.4 Conclusion

We have shown that mpMRI is a useful tool in diagnosing localised radiorecurrent cancer. As certain studies have shown that radiorecurrent prostate cancer (64,111) may have a dominant focus and this may be amenable to focal therapy. It is important to be able to characterize this accurately using the best imaging and biopsy techniques that could further guide targeted therapy. A combination of mpMRI and Template mapping biopsy may be the best technique to predict those suitable for focal therapy.

4.3 Radiorecurrent prostate cancer features on template biopsy: Implications for focal salvage therapy

4.3.1 Introduction

Radiotherapy is an effective treatment for localised prostate cancer. However, approximately, one in four men who receive primary radiotherapy for localised prostate cancer may develop biochemical failure within 8 years as witnessed with rising PSA levels (8). Focal salvage therapy (FST) may be a suitable treatment method in these men who have localised recurrent disease for example using cryosurgery, HIFU or brachytherapy techniques. For this to be delivered appropriately, an accurate determination of the presence or absence of localised recurrence, and where in the gland disease resides, is necessary.

Transperineal prostate mapping (TPM) biopsy samples the entire prostate at 5mm intervals, has been shown to have high detection rates for radiorecurrent clinically significant cancer and importantly can be used as reference test for what may be present in the prostate without reverting to whole-mount pathology (45). We sought to evaluate the proportion of men presenting with presumed localized radiorecurrent prostate cancer who might be suitable for FST based on TPM biopsies.

4.3.2 Methods and Materials

Ethics committee exemption was granted by the University College London Hospitals Joint Research Office. Our TPM biopsy registry (December 2007 to May 2014) identified 145 consecutive men, referred with suspicion of radio-recurrent prostate cancer due to rising PSA following external beam radiotherapy (EBRT) or brachytherapy who subsequently underwent TPM biopsies. All men had no evidence of distant disease based on a combination of pelvic MRI, radioisotope CT/PET scans (FDG initially and later 18F-choline)

and/or bone-scan. This is the standard of care for such patients referred to our institution for consideration of local salvage therapy.

Transperineal Template Mapping Biopsy (TPM)

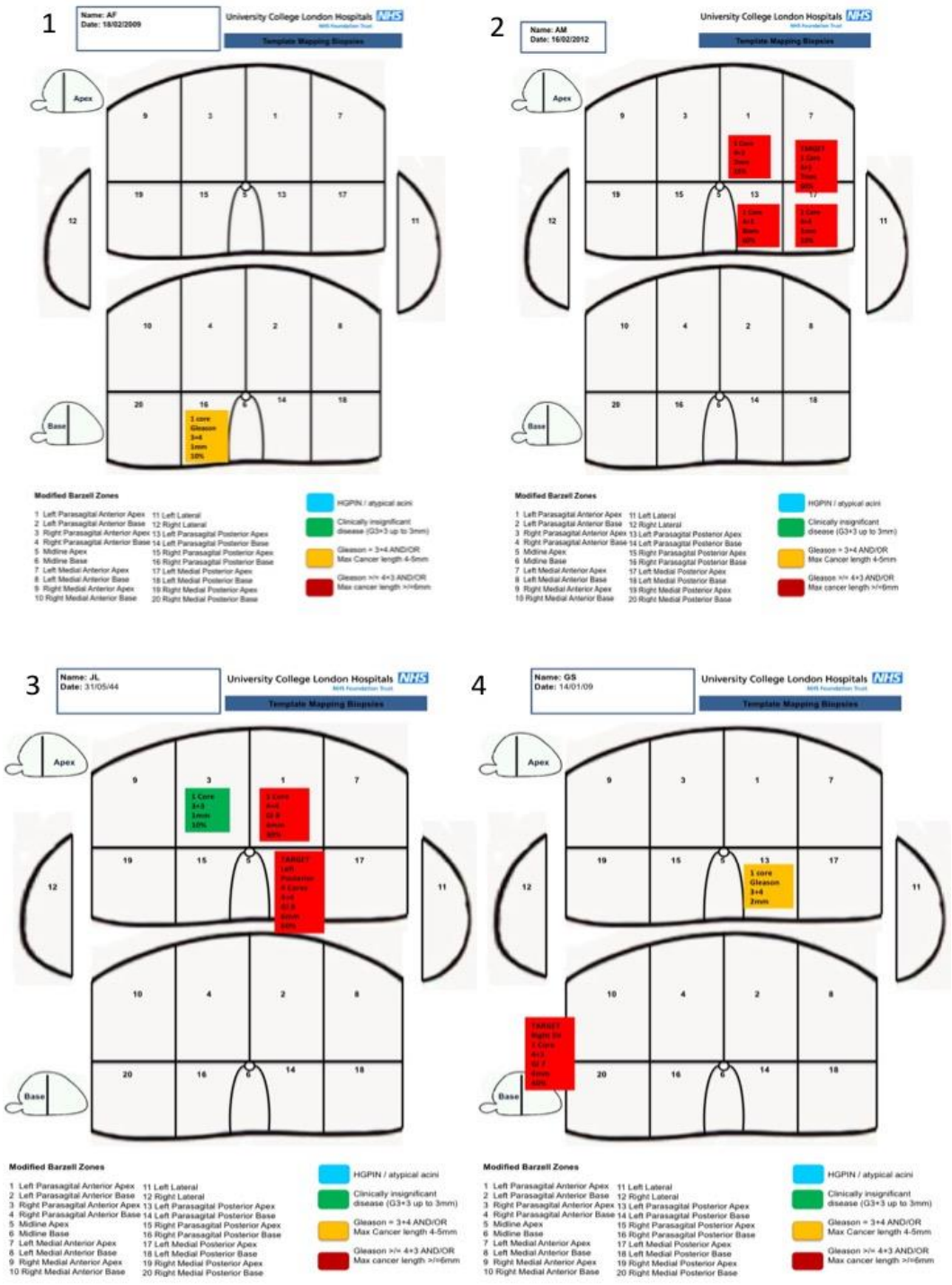
As discussed above in Chapter 4.1 Targeted transperineal prostate biopsy in the detection of radiorecurrent prostate cancer) using a modified version of that described by Barzell et al. (74). (See Figure 1 - Transperineal Prostate Mapping Modified Barzell Zones above- Chapter 4.1 Targeted transperineal prostate biopsy in the detection of radiorecurrent prostate cancer). Biopsy cores were analysed and reported by two dedicated expert uro-pathologists with over 10 years of experience in the diagnosis of prostate malignancy. Pathologists were aware of clinical details.

Antibiotic prophylaxis was used with single-dose gentamicin, cefuroxime, and metronidazole at the time of induction. Complications were assessed on review of subsequent clinic appointments.

Outcome measurements

Suitability for focal therapy required the cancer to be (1) unifocal, (2) unilateral, (3) bilateral/bifocal with at least one neurovascular bundle avoided, or (4) bilateral/multifocal with one dominant index lesion and secondary lesions with Gleason ≤3 + 3 and cancer core involvement ≤3 mm. (See Figure 7 - Type of focal salvage treatment as predicted by Transperineal Mapping biopsy)

Figure 7 - Type of focal salvage treatment as predicted by Transperineal Mapping Biopsy



1 – Quadrant ablation

2 – Hemiablation

3 – Hemi-ablation with extension across midline

4 – Index Lesion ablation

4.3.3 Statistical Analysis

Normally distributed variables are expressed as mean +/- the standard deviation. Variables with a skewed distribution are depicted as median with their corresponding interquartile range (IQR). Categorical variables are denoted as absolute numbers with percentages. Comparisons between categorical variables are done with the Pearson's $\chi 2$ test.

With univariable and multivariable logistic regression, odds radios (ORs) with 95% confidence intervals (95% CIs) were obtained to assess the influence of clinical characteristics on suitability of FST. A two-tailed $p < 0.05$ was considered statistically significant. Factors with $p<0.05$ were retained in the final model. Other factors were excluded, starting with the least significant one.

Statistical analysis was performed using SPSS version 23.0 (SPSS, IBM Corporation, New York) and the R language environment (R Core Team 2015, version 3.2.1). SPSS was used for descriptive statistics and the rms package in R for the modelling process.

4.3.4 Results

The mean age was 70.7 (SD 5.8) years with mean time from radiotherapy to biochemical failure of 64.2 (SD 34.5) months. Baseline D'Amico risk score at time of biochemical failure and prior to mpMRI and TPM was available for 121 men. Of these, 49.7% (72/121) were classified as high risk (PSA ≥ 20ng/ml, Gleason ≥8, T2c-3a), 24.8% (36/121) were intermediate risk (PSA 10-20ng/ml, Gleason 7, or T2b) and 10.7% (13/121) were low risk (PSA <10ng/ml, Gleason </=6, T1-2a) (Table 35). 17 were on hormones at the time of biopsy. Reported complications included haematospermia 0.7% (1/145), 1.4% dysuria 1.4% (2/145) and urine retention 0.7% (1/145). Baseline or follow up erectile function was not recorded.

Table 35 - Baseline characteristics and TPM-characteristics

Baseline characteristics and TPM-characteristics		
Variable	Value	Missing (%)
Age at RT (mean±sd)	70.7 (5.8)	0 (0%)
PSA at RT (median [IQR])	15.5 (8.1-30.5)	43 (29.7%)
Time between RT&BF (mean±sd)	64.2 (34.5)	38 (26.2%)
RT dose (median [IQR])	64 (55-74)	107 (73.8%)
Brachytherapy (n) (%)	15 (10.3)	NA
Stage at RT (n) (%) <T2 T3a T3b T3bN1	 44 (30.3) 14 (9.7) 14 (9.7) 3 (2.1)	70 (48.3%)
Adjuvant ADT (n) (%)	Yes 75 (51.7) No 12 (8.3)	58 (40%)
Gleason pre-RT (n) (%) 2-6 7 8-10	 47 (32.4) 49 (33.8) 23 (15.9)	26 (17.9%)
D'Amico Risk category pre-original RT Low risk (PSA <10, G <6, T1-2a) Intermediate risk (PSA 10 - 20, G7, or T2b) High risk (PSA >20, G >8, T2c-3a)	 13 (9.0) 36 (24.8) 72 (50.0)	24 (16.6%)
PSA nadir after original RT (median [IQR])	0.5 (0.12-1)	84 (57.9%)
PSA at mpMRI date (median [IQR])	4.5 (2.5-7.7)	25 (17.2%)

Prostate size on mpMRI, cc (median [IQR])	26 (19-36)	6 (4.1%)
Stage on mpMRI (n) (%) <T2 T2N1 T3a T3aN1 T3b T4	 98 (67.6) 1 (0.7) 25 (17.2) 1 (0.7) 16 (11.0) 4 (2.8)	0 (0%)
Bone scan (n) (%)	77 (53.1)	0 (0%)
Bone scan positive (n) (%)	12 (8.3)	0 (0%)
Choline-PET (n) (%)	87 (60)	0 (0%)
Type of Choline (n) (%) FDG 18F	 3 (3.4) 70 (48.2)	14 (9.7%)
Choline-PET positive (n) (%)	80 (91.9)	0 (0%)
Choline-PET positive metastases (n) (%)	20 (22.3)	1 (0.7%)
Gap between mpMRI & Biopsies (median [IQR])	2 (1-4)1	2 (1.4%)
Total no. of all cores (median [IQR])	31 (23-41)	0 (0%)
Total no. positive cores (median [IQR])	4 (1-8)	0 (0%)
% positive cores (mean±sd)	17.6 (18.1)	0 (0%)
MCCL (mean±sd)	4.7 (4)	0 (0%)
%MCCL (mean±sd)	39.7 (31.7)	10 (6.9%)

4.3.4.1 Primary outcome

Overall 75.9% (110/145) were suitable for a form of FST. 40.7% (59/145) were suitable for quadrant ablation, 14.5% (21/145) for hemi-ablation, 14.5%

(21/145) for bilateral lesion ablation and 6.2% (9/145) for index lesion ablation. 9.0% (13/145) were suitable for whole-gland treatment only. 15.9% (22/145) did not have any local recurrent disease and were deemed to have likely micrometastatic disease not visible on imaging (Table 36).

Table 36 - Proportion of patients suitable for focal salvage treatment

Type of focal salvage treatment	**N (%)**
Quadrant	59 (40.7)
Hemiablation	21 (14.5)
Bilateral	21 (14.5)
Index	9 (6.2)
Whole gland	13 (9.0)
No Treatment	22 (15.2)

4.3.4.2 Secondary outcomes

First, in terms of risk stratification using a TPM biopsy risk scoring system (99) validated in our centre, we found 3.4% (5/145) had low risk cancer (Gleason 3+3 up to 3mm) diagnosed on TPM biopsy, 17.9% (26/145) had UCL definition 2 risk cancer (Gleason =3+4 OR any grade of cancer length 4-5mm) and 63.4% (92/145) had high risk UCL Definition 1 cancer (Gleason >/=4+3 OR any grade of cancer length >/=6mm) (Table 37).

Table 37 - Transperineal Template Mapping Biopsy Outcome

Cancer detected	**% (N)**
No cancer	15.2 (22)
Low (Clinically insignificant disease Gleason 3+3 ≤ 3mm)	3.4 (5)
Intermediate (Gleason = 3+4 AND/OR Max Cancer length 4-5mm)	17.9 (26)
High Gleason >/= 4+3 AND/OR Max cancer length >/=6mm	63.4 (92)

All low risk patients were suitable for quadrant ablation. All intermediate risk patients were suitable for a form of focal salvage treatment. For high risk patients, only 14% required whole gland ablation, whilst the remainder were suitable for a form of focal salvage treatment (p=0.004 Pearson χ^2) (Table 38 & 39).

Table 38 - The relationship of suitability for focal therapy and risk groups following transperineal template prostate-mapping biopsies

		Type of Treatment					
		No treatment N (%)	Quadrant N (%)	Hemi ablation N (%)	Bilateral N (%)	Whole gland N (%)	Index N (%)
Outcome of template biopsy	No cancer	22 (15)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Low Risk	0 (0)	5 (3.4)	0 (0)	0 (0)	0 (0)	0 (0)
	Intermediate Risk	0 (0)	17 (11.7)	3 (2)	4 (2.8)	0 (0)	2 (1.4)
	High Risk	0 (0)	37 (25.5)	18 (12.4)	17 (11.7)	13 (9.0)	7 (4.8)
	Total	22 (15)	60 (41.3)	21 (14.4)	21 (14.4)	13 (9.0)	9 (6.2)

Table 39 - Relationship between suitability for focal salvage and risk group based on TPM biopsies – All risk groups

Risk category based on TPM biopsies	Suitable for focal salvage	Unsuitable for focal salvage	p-value (test)
No cancer	0	23	0.004 (Pearson χ^2)
Low risk	5	0	
Intermediate risk	22	4	
High risk	62	29	
No cancer	0	23	0.002 (Pearson χ^2)
Low + intermediate risk	27	4	
High risk	62	29	

Second, on both univariate and multivariate analyses, high risk versus low and intermediate risk groups combined predicted suitability for whole-gland salvage treatment OR 5.85 [95% CI 2.13-20.67, p=0.002] and 4.03 [1.18-16.81 p=0.035]), respectively. On univariate analysis, total number of positive cores and maximum cancer core length had an OR of 1.14 (95% CI 1.07-1.22, p=<0.0001) and 1.21 (95% CI 1.09-1.34, p=0.0002), respectively, of predicting suitability for whole-gland salvage treatment (Table 40).

Table 40 – Univariable and Multivariable analysis predicting likelihood for whole gland salvage treatment

Variable	Univariable OR (95% CI)	P value	Multivariable OR (95% CI)	P value
Age	0.99 (0.93-1.06)	0.78	NA	NA
PSA at RT	0.997 (0.974-1.016)	0.79	NA	NA
Time between RT and BF	1.00 (0.987-1.013)	0.97	NA	NA
RT dose	1.03 (0.98-1.10)	0.27	NA	NA
Stage at RT (reference <T2) T3A T3B T3BN1	 0.50 (0.07-2.23) 0.82 (0.16-3.22) 6.00 (0.53-136.76)	 0.41 0.76 0.16	NA	NA
Adjuvant ADT	1.58 (0.37-10.89)	0.58	NA	NA
Gleason score before RT Gleason 7 Gleason 8-10	 1.22 (0.45-3.36) 2.71 (0.89-8.39)	 0.69 0.08	NA	NA
Risk category pre-RT (reference=low risk) Intermediate High	 1.83 (0.39-13.31)	 0.48 0.46	NA	NA

	1.83 (0.44-12.57)			
Nadir after primary RT	1.14 (0.44-2.56)	0.76	NA	NA
PSA at mpMRI	1.00 (0.97-1.015)	0.98	NA	NA
Prostate size on mpMRI	0.972 (0.938-0.998)	0.08	NA	NA
Overall detection on mpMRI (per point increase on Likert scale)	1.55 (0.98-2.45)	0.06	NA	NA
SV involvement	1.46 (0.85-2.53)	0.16	NA	NA
mpMRI stage T2N1 T3A T3AN1 T3B T4	NS (p=0.99, 0.49, 0.99, 0.75, 0.87)		NA	NA
Time between mpMRI and TGB	0.86 (0.71-1.023)	0.09	NA	NA
Total No. cores TPM	1.025 (1.00-1.05)	0.05	NA	NA
Total No. positive cores on TPM	1.14 (1.07-1.22)	<0.0001	1.05 (0.95-1.16)	0.30
% positive	1.05 (1.03-1.08)	<0.0001	1.03 (0.99-1.07)	0.11
MCCL mm	1.21 (1.09-1.34)	0.0002	1.00 (0.87-1.15)	0.96
MCCL %	1.02 (1.01-1.04)	0.0007	NA	NA
Gleason score before salvage (low risk as			NA	NA

reference) Intermediate risk (Gleason 7) High risk (Gleason 8-10)	2.13 (0.34-4.14) 3.00 (0.43-6.07)	0.50 0.34		
High risk versus low+intermediate+no cancer	5.85 (2.13-20.67)	0.002	4.03 (1.18-16.81)	0.035

4.3.5 Discussion

4.3.5.1 Summary of results

In summary, we have shown that in men presenting with biochemical recurrence following radiotherapy for treatment of non-metastatic prostate cancer who have presumed localised recurrence based on imaging, just over two-thirds were suitable for a form of focal salvage treatment. We also found that higher risk radiorecurrent as well as greater burden of cancer in the prostate (number of positive cores and amount of cancer per core) were factors in predicting cases that were not suitable.

4.3.5.2 Methodological Limitations

First, our tertiary referral base might have led to selection biases that we are not aware of such as PSA kinetics and co-morbidity judgements made by the referring oncologist. Second, these findings only apply to those men who have a negative metastatic screen with imaging and not the whole radiorecurrent group. Third, the concept of an index lesion in the radiorecurrent setting is controversial although longitudinal studies following index lesion ablation will determine clinical significance of untreated lesions and tissue. Finally, we accept that there is some debate around the histological grading of radiorecurrent cancer. After radiotherapy there can be delayed tumour

regression and conversion to negative biopsies at a mean time of 30 months (100) (23). Within our study the average time between radiation therapy and repeat biopsy was 82.5 months (SD 35.0). There were only 2 patients that were biopsied before 30 months. Further, our histopathologists have over ten years' experience in identifying radiorecurrent prostate cancers and associated Gleason grades when there is minimal treatment effect seen microscopically.

4.3.5.3 Comparison with other studies

As discussed previously, in order for men to be suitable for focal salvage therapy, radiorecurrent disease must be accurately characterized. This must be done with accurate imaging and biopsy technique. We have previously discussed the accuracy of MRI and TPM, therefore this will only be discussed briefly now. Whilst mpMRI has been reported to have high sensitivity and specificity of up to 86-100% (43,94) for the detection of radiorecurrent cancer, these studies have used transrectal ultrasound biopsy, which is known to miss disease. One study examining mpMRI using TPM biopsy, found an accuracy (area under receiver operating characteristic curve, AUROC) of up to 0.89 and higher risk cancers (≥3mm biopsy cancer core length) of AUROC 0.93 (44). Our previous study above has shown TPM to detect 85.7% of clinically significant radiorecurrent cancers (UCL Definition 2 disease). There was a similar detection rate on TPM of UCL Definition 1 cancers compared with MRI-TB as shown above in section 4.1 (68% vs.71%) (45).

This is the first study, however to correlate TPM outcomes with baseline and pre-salvage risks to determine suitability for focal salvage therapy.

4.3.5.4 Clinical implications

Our current study has further examined the utility of TPM biopsy in determining eligibility and planning for focal salvage treatment and we have shown that a large portion of our cohort (69%) was suitable for a form of focal

salvage treatment. We have used the same TPM risk classification of cancer within the prostate (UCL definitions low, intermediate and high risk prostate cancer) as in the primary setting (99). This has not been validated in the radiorecurrent setting. It may be argued that intermediate risk cancer should be classified as high-risk cancer. Further, high risk radiorecurrent disease despite possibly being suitable for focal salvage treatment, may have a higher risk of micro-metastatic disease and therefore it is questionable whether these men receive further local treatment (112). It could be argued that these men should receive whole gland treatment given the aggressive nature of disease, albeit at a cost of increased morbidity.

4.3.5.5 Future Research

The question about whether focal salvage therapy is a valid option is currently subject to a number of prospective studies including FORECAST (FOCal RECurrent Assessment and Salvage Treatment) study (clinicaltrials.gov number: NCT01883128) (113). Further comparative studies might also be required although the ability for the uro-oncology and urology fraternity to randomise in these settings has so far proven to be limited (114). It is also clear that a risk classification of local radiorecurrent cancer should be developed. This will help classify patients and provide them with the most suitable form of salvage treatment.

4.3.6 Conclusion

Men who fail radiotherapy may be suitable for focal salvage treatment. Accurate characterisation of radiorecurrent disease is necessary. Using transperineal template prostate biopsies has shown that over two-thirds of men with presumed localised recurrence might be suitable for a focal approach to salvage their disease. The effectiveness of focal salvage therapy is still to be determined in prospective clinical trials.

Chapter 5 Salvage Treatment

This section examines the outcomes of focal salvage HIFU in a retrospective registry analysis. The latter discusses the early outcomes of focal salvage HIFU and focal-salvage cryotherapy from The FORECAST trial.

5.1 Focal Salvage HIFU

5.1.1 Introduction

Up to half of the men who have localized prostate cancer treated with radiotherapy may experience biochemical failure (BCF) by 5–10 years (3,87,115). Due to inadequate patient selection, most are treated with androgen deprivation therapy (ADT), a palliative treatment strategy which carries significant side effects (12,115-117). When curative salvage is possible, whole-gland salvage therapies are usually performed. These salvage therapies include radical prostatectomy (RP), brachytherapy, cryosurgery and high-intensity focused ultrasound (HIFU). Biochemical disease-free survival (b-DFS) rates at 5 years of up to 82% have been reported; however, these therapies can have significant side effects, such as urinary incontinence (21–90%), impotence (in those who still had erections; 100%) and rectal injury (9.2%) (12,115) . Focal salvage therapy aims to treat the area of recurrent disease rather than the entire prostate gland. A recent review has shown promising biochemical control rates and low side effects of such focal strategies, including cryotherapy and HIFU, strategies considered experimental by the European Association of Urology (118,119).

The aim of the present study was to assess cancer control rates and genito-urinary and rectal complications of focal salvage HIFU (FS-HIFU) treatment.

5.1.2 Methods and Materials

Patient Selection

Analysis of an independent prospective academic HIFU registry at two centres (University College London Hospitals and NHS Basingstoke Trust) identified 150 men who underwent focal salvage HIFU between November 2006 and August 2015. These patients' records were retrospectively reviewed to obtain data from their external referral centre on disease localization, treatment and follow-up. Institutional review board exemption was granted by the University College London Hospitals/University College London Joint Research Office. To be eligible for focal salvage HIFU, all patients had to have experienced BCF according to the Phoenix definition (PSA nadir + 2.0 ng/mL) before subsequent diagnostic methods were adopted.

Disease Localization

Before patients are considered for salvage treatment at our institutions, metastatic disease must be excluded using bone scan and positron-emission tomography (PET) imaging (Choline-18F-FDG PET or Choline PET/CT) and pelvic MRI for nodal staging. There were no restrictions placed on the upper level of PSA or PSA kinetics, provided the imaging scans confirmed ≤T3bN0M0 disease. We included T3b tumours if <1 cm of the seminal vesicle was involved. Disease was localized using prostate multiparametric MRI (mpMRI) studies. The prostate was divided into four sectors in three sections (base, mid-gland, apex), with the urethra as the anatomical dividing point between right and left and anterior and posterior. Each of the 12 resulting sectors and seminal vesicles were scored using the five-point Likert scale (1, highly likely no tumour; 5, highly likely tumour). The sequences were evaluated in the following manner. First, the T2 sequences were used to provide morphology and anatomical localization. DCE images played a greater role in the peripheral zone, with the additional reference of the DWI scans. Scoring was as follows: a score of 1 or 2 was given if there was no enhancement; a score of 3 was given if symmetrical diffuse enhancement was

seen; if there was focal or asymmetrical enhancement ≥3 mm and no abnormality seen on DWI, a score of 4 was given; and if there was focal or asymmetrical enhancement ≥3 mm and/or corresponding DWI abnormality in the same anatomical location, a score of 5 was recorded. A similar technique was used to report lesions in the transition zone, with DWI sequences given greater weighting than DCE images. DCE shows more enhancement of adenomas in this zone, especially after radiotherapy; however, an equivocal score of 3 based on DWI could be upgraded to 4 or 5 if there was an associated obvious DCE abnormality in the same anatomical location.

Patients then had either systematic TRUS-guided biopsies or transperineal template prostate mapping (TPM) biopsies using a 5-mm sampling frame. The group who had been diagnosed via TRUS biopsy underwent hemi-ablation salvage HIFU when mpMRI showed a unifocal recurrence at the same site as the positive biopsy. This extended treatment volume was adopted because of insufficient location assessment with systematic TRUS-guided biopsies and the subsequent difficult matching with the recurrence location on MRI.

HIFU Treatment

Using the Sonablate 500 transrectal HIFU device (Sonacare Inc, Focus Surgery, Indianapolis, IN, USA), treatment was either focal (quadrant) ablation, hemi-ablation, or index lesion ablation (Figure 2 Methods of focal ablation). Index lesion ablation was performed if there was multifocal cancer, any untreated areas had ≤1 core with ≤3 mm Gleason 3 + 3 disease (on TPM) and/or no lesion on mpMRI. A margin of 5 mm was adopted around the MRI-based tumour delineation.

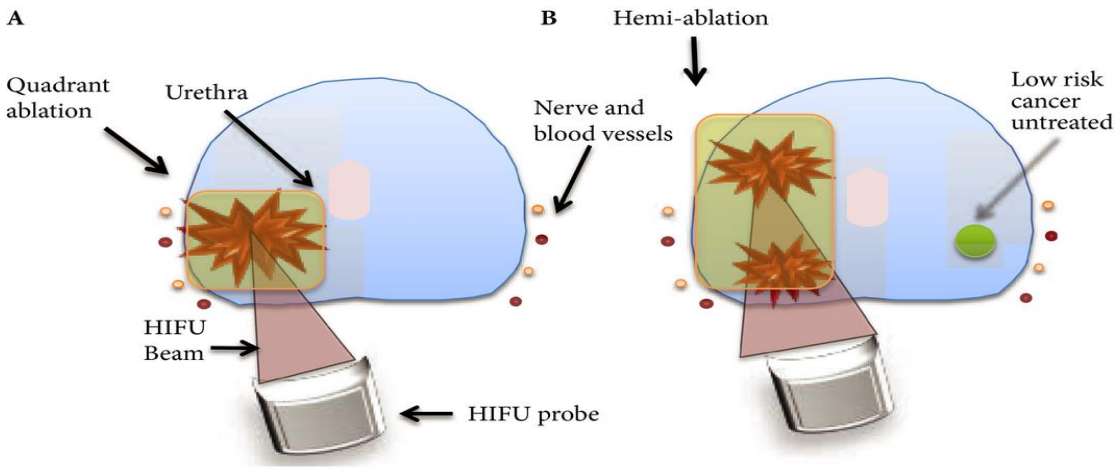


Figure 2 - Methods of focal ablation (A) Posterior quadrant salvage ablation to a single lesion with focal salvage high-intensity focused ultrasound (HIFU). (B) Hemi-ablation of index lesion to two index lesions with focal salvage HIFU whilst leaving low-risk cancer untreated.

Follow-Up

Clinical visits occurred every 3 months to record adverse events and serum PSA level. Validated questionnaires were issued to all patients and included the IPSS, the urinary domain of the University of California Los Angeles-Expanded Prostate Cancer Index Composite (UCLA-EPIC), and the five-item International Index of Erectile Function (IIEF-5) (120,121) . A higher IPSS indicates worsening symptoms, a lower UCL-EPIC score indicates worsening symptoms, and a lower IIEF-5 score indicates worsening erectile function. Any two consecutive rises in PSA level were investigated using mpMRI and, if mpMRI was positive, by further biopsies and/or staging scans, including bone-scan or Choline PET/CT or both.

5.1.3 Outcomes

5.1.3.1 Primary outcomes

The primary outcome was a composite failure rate after one or two focal salvage HIFU procedures (BCF and/or positive localized or distant imaging and/or positive biopsy and/or systemic therapy and/or metastases and/or prostate cancer-specific death).

5.1.3.2 Secondary Outcomes

The secondary outcome consisted of BCF using the Phoenix-ASTRO definition (nadir PSA + 2 ng/mL) after one or two focal salvage HIFU procedures, and complications/side effects. We also assessed several factors predicting BCF, including baseline (before primary radiotherapy) D'Amico risk group, PSA level, T stage, Gleason score, external beam radiation therapy (EBRT) dose and ADT use. Predictive factors before focal salvage HIFU included PSA nadir after primary radiotherapy, T stage, prostate volume on MRI, Gleason score, maximum cancer core length, PSA, PSA doubling time (PSADT), ablation type (hemi-/focal/index lesion ablation), ADT use and residual cancer left untreated. PSA nadir after focal salvage HIFU was assessed as a post-treatment factor.

Statistics

Cox proportional hazards regression was used to quantify the effect of the determinants described above on the endpoints. Hazard ratios (HRs) with 95% CIs are provided. Factors with *P* values <0.05 were included in the multivariable model. The R language environment (version 3.2.1; available at http://www.r-project.org/) (122) was used for all statistical analyses.

5.1.4 Results

A total of 150 patients underwent focal salvage HIFU for radiorecurrent prostate cancer between November 2006 and August 2015 (Tables 41 and 42). Of these, 20.7%, 23.3% and 42.0% had low-, intermediate- and high-risk disease prior to radiotherapy (14% missing). A total of 96.7% of the patients underwent EBRT and 3.3% underwent EBRT with a high-dose-rate brachytherapy boost. Radiation doses of 64 Gray in 32 fractions were the most common (*n* = 27). The median time to BCF from primary radiotherapy was 80 months (95% CI 72–86). The mean (SD) age at focal salvage therapy was 69.8 (6.1) years and the median (interquartile range [IQR]) PSA level before focal salvage treatment was 5.5 (3.6–7.9) ng/mL. Prior to focal salvage HIFU, metastatic disease was excluded by bone scan or Choline PET/CT/FDG scan. Some patients underwent a 18F-Choline FDG PET, but this was earlier in the series before clinical practice was changed so that 18F-Choline PET/CT was performed instead. All patients underwent mpMRI and either TPM (*n* = 104) or TRUS biopsy (*n* = 40, with one patient undergoing MRI-guided biopsies (Table 42). From May 2012 onwards, most patients underwent TPM biopsies (~85%), while this was ~65% before that time. The choice of biopsy was made at the discretion of the treating physician, but a clear temporal trend to more TPM biopsies was observed.

Table 41 Characteristics before primary radiation treatment

Characteristics before primary radiation treatment	**Primary therapy, *n* (%)**	**Missing, %**
EBRT	145 (96.7)	0
EBRT + HDR-BT boost	5 (3.3)	0
Median (IQR) initial PSA before primary treatment, ng/mL	13.9 (8.9–26.3)	10

D'Amico risk group, *n* (%)		
High: PSA 20 ng/mL, Gleason score ≥8 and T2c–T3a	63 (42)	
Intermediate: PSA 10–20 ng/mL), Gleason score 7 or T2b	35 (23.3)	14
Low: PSA <10 ng/mL, Gleason score ≤6 and T1–2a	31 (20.7)	
ADT use (cytoreduction/adjuvant or neoadjuvant)	106 (71)	1.3
ADT, androgen deprivation therapy; BT, brachytherapy; EBRT, external beam radiotherapy; HDR, high-dose-rate; IQR, interquartile range.		

Table 42 Patient characteristics before focal salvage high-intensity focused ultrasound

Characteristic		**Missing, %**
Mean ± SD age at focal salvage treatment, years	69.8 ± 6.1	0
Median (IQR) PSA pre-salvage, ng/mL	5.5 (3.6–7.9)	0.7
Radiological T stage pre-salvage HIFU, *n* (%)		
T1	11 (7.3)	1.3
T2	102 (68)	
T3	35 (23.3)	
Gleason grade pre-salvage HIFU, *n* (%)		
Gleason 2-6	8 (5.3)	2.7

Gleason 3 + 4	72 (48)	
Gleason 4 + 3	39 (26)	
Gleason 8–10	27 (18)	
Biopsy type, *n* (%)		
TPM	104 (69.3)	3.3
TRUS-guided	40 (26.7)	
MRI-guided	1 (0.7)	
D'Amico risk group pre-salvage HIFU, *n* (%)		
High: PSA >20 ng/mL, Gleason score ≥8 and T2c–T3a	62 (41.3)	16.7
Intermediate: PSA 10–20 ng/mL, Gleason score 7 or T2b	59 (39.3)	
Low: PSA <10 ng/mL, Gleason score ≤6 and T1–2a)	4 (2.7)	
ADT pre-salvage HIFU, *n* (%)	68 (45.3)	0
ADT, androgen deprivation therapy; HIFU, high-intensity focused ultrasound; IQR, interquartile range; TPM, template prostate mapping; Tx, treatment.		

Low-, intermediate- and high-risk disease using D'Amico classification, was present in 2.7% (4/150), 39.3% (59/150) and 41.3% (62/150) of patients prior to focal salvage HIFU (missing, 16.7% (*n* = 25)). Three forms of ablation were performed (Table 43): focal ablation 55% (82/150), hemi-ablation 34% (51/150) and index lesion ablation 11% (17/150). A total of 45.3% of patients (68/150) were receiving ADT (anti-androgen) and this was discontinued 6–8 weeks after HIFU. A total of 13 patients received a second focal salvage HIFU procedure for localized recurrence after primary focal salvage HIFU. The recurrence was based on mpMRI and TPM biopsy in four patients, TPM biopsy with negative mpMRI in two patients, mpMRI alone in four patients and TPM biopsy alone in three patients.

Table 43 Outcomes after focal salvage high intensity focused ultrasound

Outcome		**Missing %**
Method of ablation		
Focal	82 (55)	0
Hemi	51 (34)	
Index lesion (with residual cancer left untreated)	17 (11)	
Composite endpoint: BCF, ADT, MRI+, biopsies + systemic treatment + metastases +, prostate cancer specific mortality, *n*(%)	91 (60.7)	0
BCF*, *n* (%)	77 (51.3)	0
Median (IQR) PSA-nadir after salvage HIFU, ng/mL	0.67 (0.2–1.9	2.7
Median (IQR) follow-up after salvage HIFU, months	35 (22–52)	0
Mortality, *n* (%)	9 (6)	0
Overall	5 (3.3)	
Prostate cancer-specific	4 (2.7)	

1. ADT, androgen deprivation therapy; BCF, biochemical failure; HIFU, high-intensity focused ultrasound; IQR, interquartile range.
2. *Phoenix definition

5.1.4.1 Primary Outcome

Composite failure occurred in 61% of patients (91/150) (see Fig. 2). The Kaplan–Meier composite endpoint free survival (CEFS) rate at 3 years was 40% (95% CI 31–50) for the entire group. Kaplan–Meier estimates of CEFS were 100%, 49% and 24% at 3 years in the low-, intermediate- and high-risk groups, respectively, before salvage therapy. When assessing CEFS in PSA responders (post-treatment PSA level ≤0.5 ng/mL) alone, the estimated CEFS rate at 36 months was 67% (95% CI 53–82).

5.1.4.2 Secondary Outcomes

A total of 51% of patients (77/150) experienced BCF. The Kaplan–Meier b-DFS rate at 3 years was 48% (95% CI 39–59) for the entire group. Kaplan–Meier estimates of b-DFS were 100%, 61% and 32% at 3 years in the low-, intermediate- and high-risk groups, respectively, before salvage therapy. A total of 43.3% of patients (65/150) were PSA responders, achieving a PSA nadir of ≤0.5 ng/mL, while 59.3% (89/150) achieved a nadir of ≤1 ng/mL. When assessing BCF in PSA responders alone (PSA nadir ≤0.5 ng/mL), BCF occurred in 12% of patients (18/150) and the estimated actuarial b-DFS rate at 36 months was 78% (95% CI 67–92). The b-DFS rate at 2 years in patients who underwent re-do HIFU, was 66% (95% CI 43–100%). The additional 36-month Kaplan–Meier estimates regarding the primary and secondary outcomes are provided in Table 6.

Of the patients with BCF, 62 underwent mpMRI in the follow-up, 13 of whom had negative results. Of the 15 patients who did not undergo mpMRI during the follow-up, one died from disease unrelated to prostate cancer or the HIFU treatment, eight received ADT (three as a result of metastatic disease on a bone-scan and/or CT and one based on positive TPM biopsies). In six patients follow-up data were insufficient to assess the procedures after BCF. Of the 49 patients with a recurrence on mpMRI, all underwent either pelvic CT or radioisotope bone scan to exclude metastatic disease. Patients potentially

eligible for a second focal salvage HIFU procedure underwent subsequent TPM biopsies in all but four cases.

Systemic therapy was initiated in 40.7% of patients (61/150), 6.7% of patients (10/150) had a positive biopsy and 9.5% (9/150) developed distant metastases. A total of 2.7% of patients (4/150) died from prostate cancer. The mean (±SD) time to ADT after HIFU was 20 (±15.9) months.
A total of 12% of patients (18/150) underwent biopsy after HIFU. This was positive in 55.6% of patients (10/18); of these 10 patients, two underwent salvage radical prostatectomy, one received ADT and then proceeded to have salvage radical prostatectomy and three were started on ADT. Overall, further treatment was performed in 12 patients: salvage radical prostatectomy (*n* = 3); EBRT to spinal metastatic disease (*n* = 1); irreversible electroporation (*n* = 1); cryotherapy (*n* = 1); chemotherapy (*n* = 4); and other drug therapy (*n* = 2). There were nine deaths overall, four of which were prostate cancer-related. The Kaplan–Meier overall survival estimate at 60 months was 92% (95% CI 85–99). One patient was in the high-risk group prior to radiotherapy and had Gleason 3 + 4 T3b disease before undergoing focal salvage HIFU. After HIFU his PSA level continued to rise, he was started on hormone treatment and went on to receive further EBRT. A second patient had intermediate-risk disease before radiotherapy and Gleason 4 + 4 and T3a disease before hemi-ablation salvage HIFU. After HIFU his PSA nadir was 0.0 ng/mL, he developed BCF 15 months later and went on to develop metastases 37 months later. A third patient had high-risk disease before radiotherapy and had PSA 4.12 ng/mL, Gleason 4 + 3, and T3a disease before focal salvage HIFU. After HIFU his PSA level rose to 5.63 ng/mL and he was started on hormone therapy and subsequent chemotherapy 24 months later. The fourth patient had high-risk disease at baseline and had a PSA level 7.26 ng/mL, Gleason 4 + 5 and T2b disease before undergoing hemi-ablation salvage HIFU. After HIFU his PSA nadir was 0.11 ng/mL and he developed BCF 9 months later and was started on chemotherapy at 54 months.

5.1.4.3 Complications

Complications included UTI in 11.3% of patients (17/150), epididymitis in 1.3% (2/150), bladder neck strictures in 8% (12/150), rectourethral fistula after first HIFU in 2% (3/150) and osteitis pubis in 0.7% (1/150). For the patients who experienced recto-urethral fistula, one spontaneously resolved, one was managed with urinary diversion with suprapubic catheter and one was surgically repaired (Table 44).

Table 44 – Clavien- Dindo Classification of Surgical Complications

Clavien- Dindo Classification of Surgical Complications	
1 Any deviation from the normal intra-operative or postoperative course, including the need for pharmacological treatment other than antiemetics, antipyretics, analgesics, diuretics, electrolytes or physiotherapy	19 (12.7)
2 Complications needing only the use of i.v. medications, total i.v. nutrition, or blood transfusion	0 (0)
3a Complications needing surgical, endoscopic or radiological intervention under local anaesthesia	25 (16.3)
3b Complications needing surgical, endoscopic, or radiologic intervention under general anaesthesia	16 (11)
4a Life-threatening complications requiring intensive care unit management: single-organ dysfunction	0 (0)
4b Life-threatening complications requiring intensive care unit management: multiorgan dysfunction	0 (0)
5 Death of the patient	*0* (0)

In patients with available data from pre- and post-HIFU functional questionnaires (UCLA-EPIC, IPSS and IIEF-5), of those pad-free at baseline, 87.5% (42/48) remained pad-free at 2 years. A total of 70.8% (34/48) had drip-free urinary continence at baseline and 67.6% (23/34) remained drip-free postoperatively at 2 years. Baseline IIEF scores were available for 31

patients: 38.1% (12/31) reported a baseline score >2 for question 2 of the IIEF, which meant that erections were mostly sufficient for penetration, and 58.3% (7/12) still had score of >2 at follow-up (Table 45).

Table 45 Functional Outcomes

Functional outcomes	**Pre-focal salvage HIFU**	**Post-focal salvage HIFU (6–36 months)**
Median (IQR) IPSS	8 (4–15)	11 (7–18)
Drip-free status, % (*n*/*N*)	67 (50/75)	46 (28/61)
Pad-free status, % (*n*/*N*)	97 (70/72)	78 (46/59)
IIEF Q2 score >2, % (*n* = 31)	38 (*n* = 12)	22 (*n* = 7)
Median (IQR) IIEF score	15 (7–39) (*n* = 54)	13 (7–24 months) (*n* = 42) (3–72 months)
PDE-5 use, % (*n*/*N*)	21 (12/57)	24 (11/45)

5.1.4.4 Univariable and Multivariable Analyses for Composite Endpoint

In univariable analyses, components that achieved statistical significance for the composite endpoint included primary Gleason score 8–10 HR 1.88 ([95% CI 1.06–3.32]; *P* = 0.03), time to radiological recurrence HR 0.989 ([95% CI 0.982–0.996]; *P* = 0.002), T stage 3 vs T stage 1 and 2 before salvage HIFU

HR 1.70 ([95% CI 1.09–2.65]; *P* = 0.02), pre-salvage HIFU PSA HR 1.06 ([95% CI 1.02–1.11]; *P* = 0.004), D'Amico pre-salvage high risk vs low risk HR 2.57 ([95% CI 0.89–7.38]; *P* = 0.08) and PSA-nadir post-salvage HR 1.26 ([95% CI 1.19–1.32]; *P* < 0.001).

In multivariable analyses components that achieved statistical significance for the composite endpoint included T stage 3 vs T stage 1 and 2 pre-salvage HIFU HR 1.96 ([95% CI 1.13–3.39]; *P* = 0.02) and PSA-nadir post-salvage HIFU HR 1.29 ([95% CI 1.20–1.38]; *P* < 0.001). The CEFS rate at 36 months (Table 46) in those with a pre-salvage HIFU PSADT of ≥12 months was 51% (95% CI 37–70) compared with 24% (95% CI 14–41; *P* = 0.003) in those with a PSADT of <12 months (Fig. 2A) and 51% (95% CI 39–67) vs 31% (95% CI 21–46; *P* = 0.002) in men with a pre-salvage HIFU PSA level <5 ng/mL compared with those with a pre-salvage HIFU PSA level ≥5 ng/mL (Fig. 2B). For patients with MRI prostate volume < 25 mL rates of CEFS at 36 months were 48% (95% CI 35–65) vs 34% (95% CI 24–49; *P* = 0.13) in those with MRI volume ≥25 mL (Fig. 2C). In men with a PSA nadir after salvage HIFU of <0.5 ng/mL CEFS at 36 months was 67% (95% CI 53-82) vs 21% (95% CI 13–33; *P* < 0.001) in those with PSA nadir ≥0.5 ng/mL (Fig. 2D).

Table 46 Kaplan-Meier estimates for composite endpoint-free survival (CEFS) rates and biochemical disease-free survival (B-DFS) rates at 36 months.

	CEFS, % (95% CI)	B-DFS , % (95% CI)
Entire group	40 (31–50)	48 (39–59)
D'Amico low risk	100 (NA)	100 (NA)
D'Amico intermediate risk	49 (36–68)	61 (48–79)
D'Amico high risk	24 (14–40)	32 (20–49)
D'Amico low + intermediate risk	51 (38–69)	62 (49–79)
D'Amico high risk	24 (14–40)	32 (20–49)
PSA nadir <0.5 ng/mL	67 (53–82)	78 (67–92)
PSA nadir ≥0.5 ng/mL	21 (13–33)	26 (17–39)

PSADT ≥12 months	51 (37–70)	60 (45–79)
PSADT <12 months	24 (14–41)	30 (19–49)
PSA <5 ng/mL	51 (39–67)	62 (50–77)
PSA ≥5 ng/mL	31 (21–46)	37 (27–53)
Prostatic volume <25 mL	48 (35–65)	60 (47–77)
Prostatic volume ≥25 mL	34 (24–49)	41 (30–56)
CEFS, composite endpoint-free survival; B-DFS , biochemical disease free survival; PSADT, PSA doubling time.		

Fig. 2 (A) Composite endpoint-free survival (CEFS) according to PSA doubling time before focal salvage high-intensity focused ultrasound (HIFU). (B) CEFS according to PSA level pre-focal salvage HIFU. (C) CEFS according to MRI prostate volume. (D) CEFS according to PSA nadir after focal salvage HIFU.

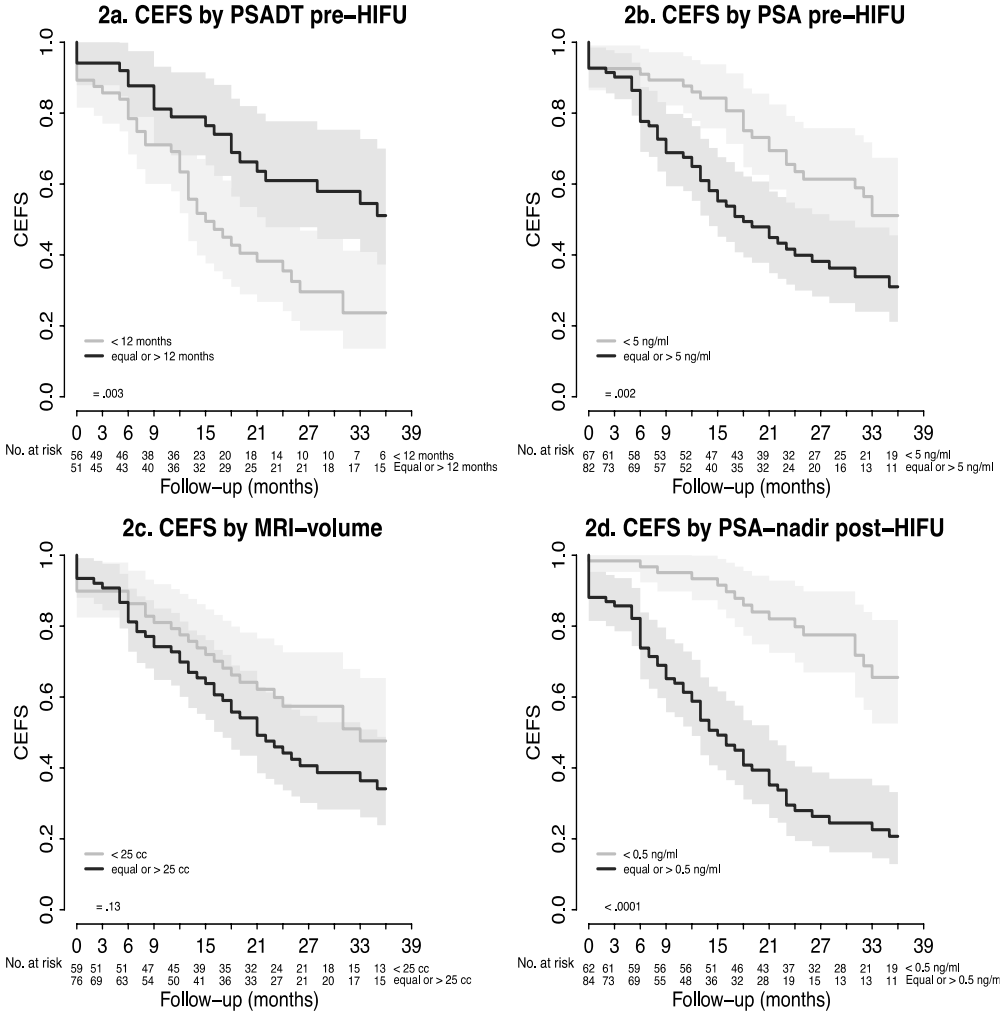
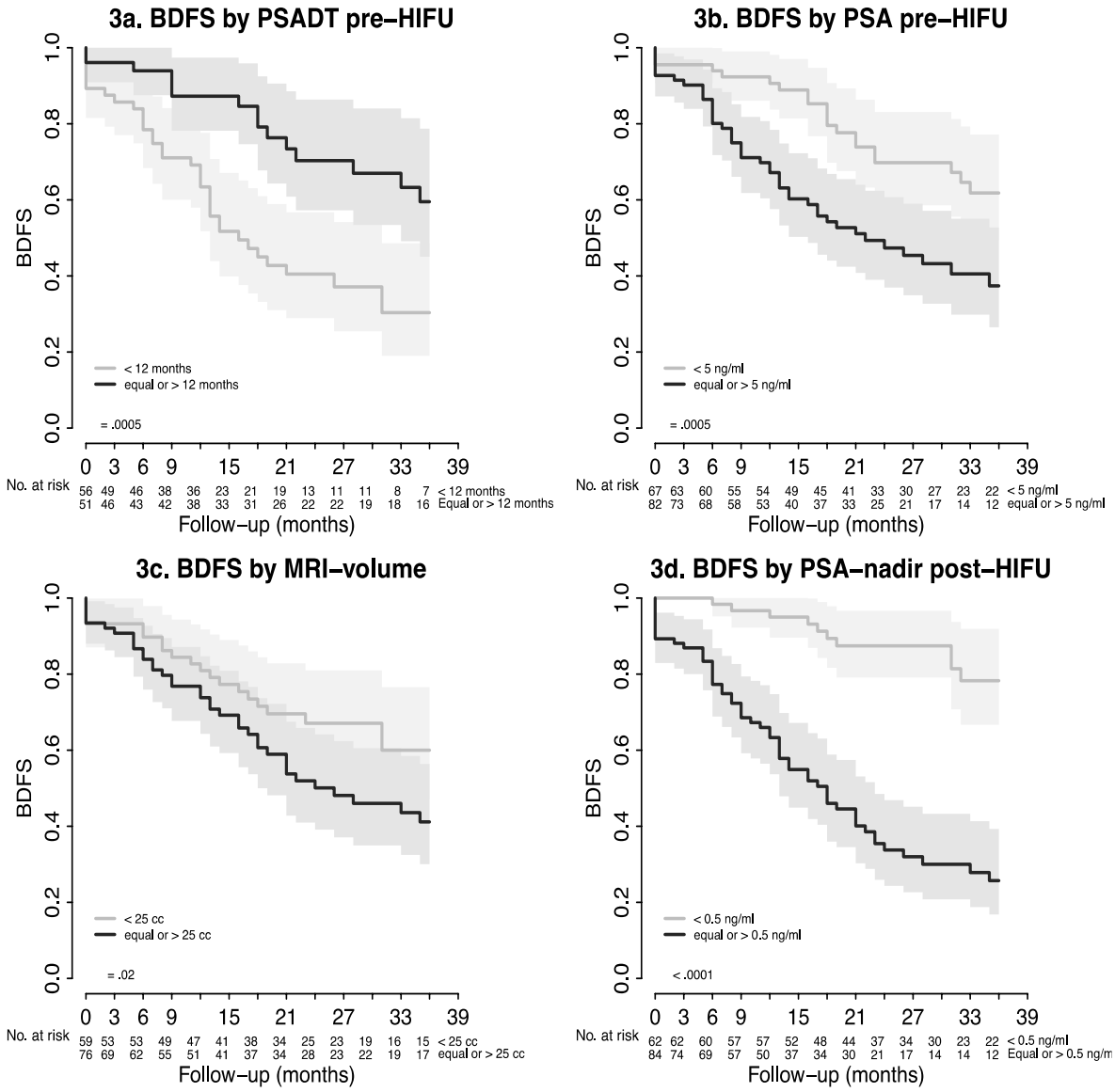


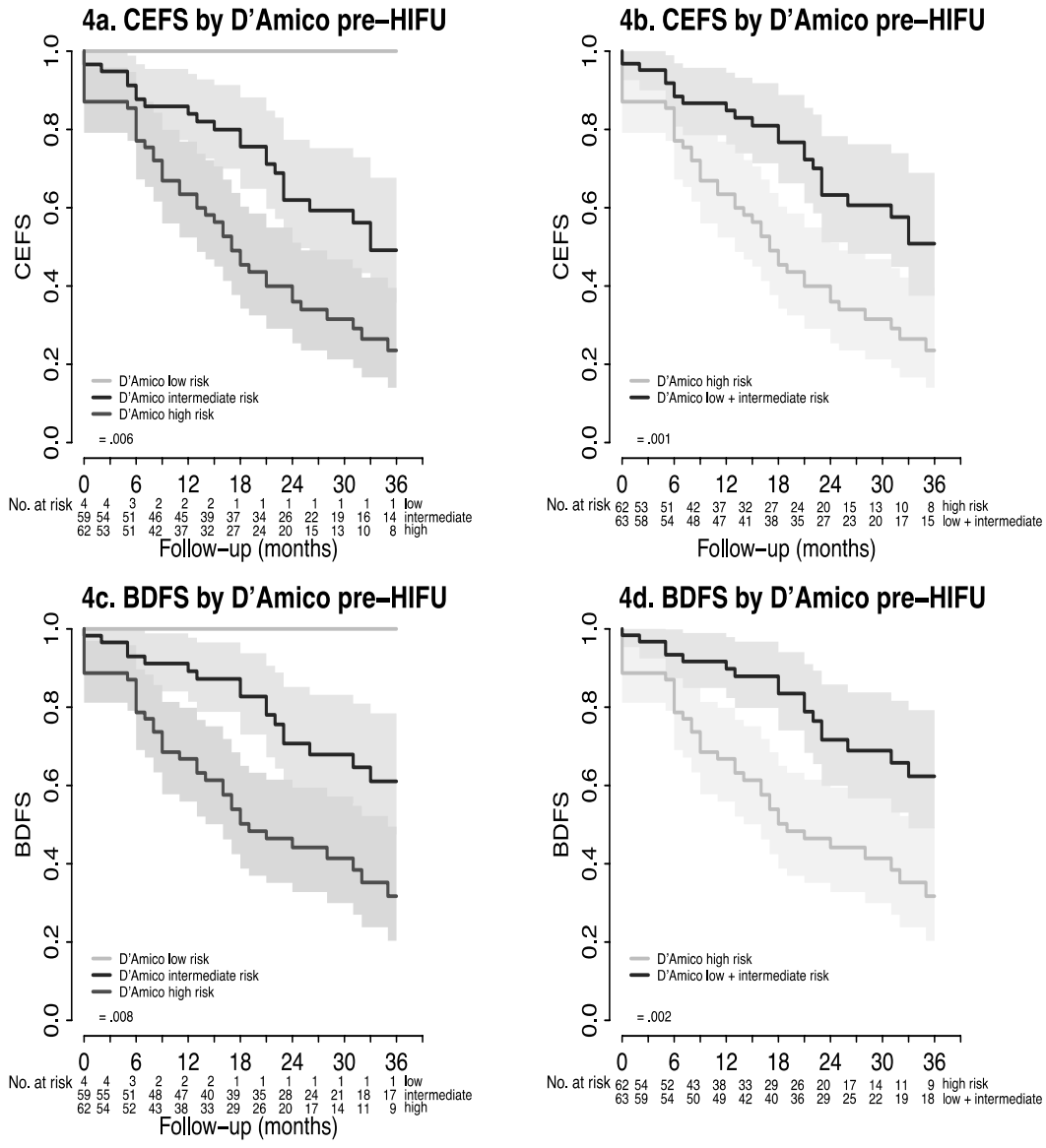
Fig. 3 (A) Biochemical disease free survival (B-DFS) rates according to PSA doubling time before focal salvage high-intensity focused ultrasound (HIFU). (B) B-DFS according to PSA level before focal salvage HIFU. (C) B-DFS according to MRI prostate volume. (D) B-DFS according to PSA nadir after focal salvage HIFU.



For the intermediate- and high-risk groups the CEFS rates at 36 months were 49% (95% CI 36–68) and 24% (95% CI 14–40; *P* = 0.006), respectively (Fig. 4A). When the low- and intermediate-risk groups were combined, CEFS

at 36 months was 51% (95% CI 38–69) vs 24% (95% CI 12–38; *P* = 0.001) for the high-risk group (Fig. 4B).

Fig. 4 (A) CEFS according to D'Amico risk classification before focal salvage high-intensity focused ultrasound (HIFU). (B) CEFS according to D'Amico low- and intermediate-risk groups combined vs high-risk group before focal salvage HIFU. (C) b-DFS according to D'Amico risk group before focal salvage HIFU. (D) b-DFS according to D'Amico low- and intermediate-risk groups combined vs high-risk group before focal salvage HIFU.



Because low-risk recurrences are uncommon, we also performed multivariable analysis after excluding patients in the low-risk group (*n* = 4); these analyses are shown in Table 47. For BCF, MRI prostate volume and PSA nadir after salvage HIFU remained statistically significant after the exclusion of patients in the low D'Amico risk group. For the composite endpoint, PSA nadir after salvage HIFU remained statistically significant.

Table 47 - Multivariable analysis for biochemical failure and the composite endpoint without D'Amico low risk patients

Determinants BF	**HR (95% CI)**	**p-value**	**Determinants CE**	**HR (95% CI)**	**p-value**
MRI volume	1.01 (1.001-1.028)	0.03			
PSA-nadir post-salvage	1.28 (1.19-1.38)	<0.0001	PSA-nadir post-salvage	1.28 (1.19-1.38)	<0.0001
Abbreviations: BF=Biochemical Failure; HR=Hazard Ratio; CI=Confidence Interval; CE=Composite Endpoint; PSADT=PSA-doubling time.					

5.1.4.5 Univariable and Multivariable Analyses for Biochemical Failure (Phoenix Definition)

In univariable analyses components that achieved statistical significance for BCF included primary Gleason Score 8–10 HR 2.06 ([95% CI 1.10–3.85]; *P* = 0.02), time to radiological recurrence HR 0.988 ([95% CI 0.980–0.995]; *P* = 0.002), T stage 3 vs T stages 1 and 2 pre-salvage HIFU HR 1.78 ([95% CI 1.11–2.87]; *P* = 0.002), MRI volume HR 1.014 ([95% CI 1.003–1.025]; *P* = 0.01), PSA pre-salvage HIFU HR 1.07 ([95% CI 1.02–1.12]; *P* = 0.003), and PSA nadir after salvage HIFU HR 1.26 ([95% CI 1.19–1.32]; *P* < 0.001).

In multivariable analyses, components that achieved statistical significance for BCF included T stage 3 vs T stages 1 and 2 pre-salvage HIFU HR 1.99 ([95% CI 1.14–3.46]; *P* = 0.02), MRI prostate volume HR 1.014 ([95% CI 1.002–1.027]; *P* = 0.03) and PSA nadir after salvage HIFU HR 1.29 ([95% CI 1.20–1.38]; *P* < 0.001).

There were significant differences in b-DFS (Table 6) at 36 months for patients with a PSADT of ≥12 months pre-salvage HIFU: 60% (95% CI 45–79) compared with 30% (95% CI 19–49; *P* < 0.001) for those with a PSADT of <12 months (Fig. 3A). For those with pre-salvage HIFU PSA <5 ng/mL vs those with PSA ≥5 ng/mL, B-DFS was 62% (95% CI 50 to −77) vs 37% (95% CI 27–53; *P* < 0.001 [Fig. 3B]). Patients with a prostate volume of <25 mL before undergoing focal salvage HIFU had a b-DFS rate at 36 months of 60% (95% CI 47–77) compared with those with prostate volume ≥25 mL, who had a b-DFS rate of 41% (95% CI 30–56; *P* = 0.02 [Fig. 3C]). At 36 months those who had a PSA nadir of <0.5 ng/mL had a b-DFS rate of 78%, (95% CI 67–92) compared with those who achieved a PSA nadir ≥0.5 ng/mL, who had a b-DFS rate of 26% (95% CI 17–39; *P*<0.001 [Fig. 3D]). For the intermediate- and high-risk D'Amico groups b-DFS rates at 36 months were 61% (95% CI 48–79) and 32% (95% CI 20–49; *P* = 0.008), respectively (Fig. 4C). When the low- and intermediate-risk groups were combined, the b-DFS rate at 36 months was 62% (95% CI 49–79) vs 32% (95% CI 20–50; *P* = 0.002) for the high-risk group (Fig. 4D).

5.1.5 Discussion

5.1.5.1 Summary of results

The present results show that focal salvage HIFU has potential in the treatment of radiorecurrent prostate cancer. In our relatively high-risk cohort, BCF occurred in 51% of patients (78/150) and composite failure in 61% (91/150). The Kaplan–Meier CEFS rate at 3 years was 40% (95% CI 31–50) for the entire group and 48% (95% CI 39–59) for b-DFS.

5.1.5.2 Methodological Limitations

A limitation of the present study is that we had limited information on baseline and postoperative erectile and urinary function, despite issuing questionnaires to most patients. Lack of baseline data may be attributable to no symptoms at initial consultation and therefore no assessment of symptoms using an objective method. Also, as this was not conducted as part of a research trial, patients were not obligated to return questionnaires, which may explain the lack of responses. As these functional data were so frequently missing, a valid conclusion is hard to link to the outcomes so far. Patients with severe deterioration might not have returned the questionnaires, thereby biasing the comparison in a significant way. Further, there is still some debate in the literature about radiation effect, delayed tumour regression and timing of biopsy after radiotherapy. Whilst there is some uncertainty, our team consists of expert uro-pathologists whose published work on clinically significant prostate cancer includes the use of different biopsy strategies in primary and radiorecurrent settings (44,99,123-125). Our experts only report a Gleason score when there is minimal radiation effect seen on the biopsies, and so feel that they are able to identify recurrent prostate cancer, when present, in radiation-affected tissues with a high degree of accuracy and to assign a grade to these.

A further limitation of the study is that no validated definition for failure is available in the (focal) salvage setting after radiotherapy failure; therefore, a composite endpoint was chosen as a combined failure definition, incorporating biochemical outcomes, imaging (mpMRI, Choline-PET/CT, radioisotope bone scan), biopsy results, systemic therapy initiation and metastatic disease/prostate cancer-specific mortality. This definition more clearly reflects failure in the early to medium term after focal salvage therapy because the Phoenix definition is not validated in the focal salvage setting and can be biased as a result of ADT use before focal salvage, which was present in a substantial number of patients (n = 68). The estimates from the Kaplan–

Meier analyses and multivariable analyses, however, are very similar for BCF and the composite endpoint, potentially indicating the validity of a failure definition based on biochemical outcomes. This is also visible in the verification of BCF with mostly MRI (*n* = 51) or biopsies (*n* = 11). Nevertheless, 13 patients still achieved the composite recurrence outcome without previous BCF. In the absence of a clear failure definition, we therefore recommend subsequent imaging and biopsy verification of patients with BCF after focal salvage HIFU.

Another limitation of the present study is the absence of detailed criteria for response assessment or adoption of subsequent diagnostic techniques in case of disease progression; however, most patients (62/77) with BCF received mpMRI in case of BCF after focal salvage HIFU. Results of mpMRI in the radiorecurrent setting are at least equal, if not better, which is hypothesized to be attributable to increased contrast of tumour with the surrounding fibrotic prostate tissue. Negative and positive predictive values of 90–95% are described (43,94,101,126,127). We have also demonstrated very high negative predictive values of a post-treatment MRI in men treated with focal HIFU who all underwent a biopsy within a clinical trial. To our knowledge, there are no results of mpMRI and/or biopsies in the setting after both radiotherapy and focal salvage HIFU in the literature.

5.1.5.3 Comparison to other studies

The present series potentially reflects higher-risk disease than other salvage series. This is observed in the median pre-focal salvage PSA level of 5.5 ng/mL in the present study. The mean/median PSA level ranges from 2.8 to 5.5 ng/mL in other focal salvage series in the literature (12), but comparisons regarding D'Amico risk groups are more difficult because this information is not usually provided in focal salvage series.
The results of the present study show that patients in the higher-risk group can also benefit from focal salvage HIFU. Even though failure is still common and subsequent treatment is initiated, in a substantial number of patients,

follow-up whole-gland or systemic treatment can be postponed or prevented and quality of life therefore potentially improved.

Excluding patients in the low D'Amico risk group (*n* = 4) further limits the patient sample and, for this reason, coincidental statistical significance cannot be excluded. The main statistical analysis was therefore performed with the low-risk group included. Furthermore, MRI prostate volume and PSA nadir after salvage HIFU remained the most significant and influential factors; therefore, exclusion of the low D'Amico risk group did not change factors associated with risk of BCF or with achieving the composite endpoint.
The present study was pragmatic in that it did not limit the entry criteria for focal salvage HIFU other than to exclude metastatic disease and substantial seminal vesicle invasion. We did not select patients on an upper threshold such as PSA level or PSA kinetics, but allowed many men with probable micro-metastatic disease to be treated. The present series therefore reflects higher-risk disease than other salvage series. As a result, we could determine more robustly the upper limit of what is possible in a focal salvage strategy for future trial design and possibly clinical practice.

Repeat treatment with a second HIFU was not classified as failure, as this was probably attributable to failure of adequate targeting during initial treatment as opposed to recurrence of disease after first focal salvage treatment. Second HIFU was therefore classified as completion of treatment. One of the key attributes for ablative therapies is repeatability, and the literature usually reports outcomes after one or two ablative therapies.

Focal salvage therapy after EBRT provides patients with a further chance at cancer control whilst potentially avoiding systemic therapies (107) and the morbidity of whole-gland salvage surgery or ablation. Salvage radical prostatectomy has been reported to have 5-year B-DFS rates of between 47 and 82% (115), complications such as rectal injury (0–28%) (115) and rates of incontinence (21–90%) (115) and erectile dysfunction (80–100%) (115) are high owing to fibrosis and poor wound healing as a result of radiation. Bladder neck strictures still occurred relatively frequently in this cohort (*n* = 12, 8%),

but this rate compares favourably with whole-gland salvage HIFU and salvage radical prostatectomy procedures, for which the bladder neck stricture rate is ~20% in the literature (12). The bladder neck stricture rate in the present study does compare somewhat unfavourably with other focal salvage series performed to date (12); however, these series had significantly fewer patients.

A systematic review of salvage focal cryotherapy found b-DFS rates of 50–68% at 3 years, recto-urethral fistula rates of 0% and erectile dysfunction rates of 60–71% (128). b-DFS rates after whole-gland salvage HIFU are 25–53% (56,57). Incontinence (10–50%), erectile dysfunction (66.2–100%) and recto-urethral fistula (3–16%) have also been reported (56,57,60). Overall, functional outcomes are generally poorly reported in the literature because of the retrospective nature of the studies.

As discussed above, there is no validated definition for failure is available in the (focal) salvage setting after radiotherapy failure. Most of our patients with BCF received mpMRI in case of recurrence after focal salvage HIFU. Results of mpMRI in the radiorecurrent setting are at least equal, if not better, which is hypothesized to be attributable to increased contrast of tumour with the surrounding fibrotic prostate tissue. Negative and positive predictive values of 90–95% are described (43,94,101,126,127). We have also demonstrated very high negative predictive values of a post-treatment MRI in men treated with focal HIFU who all underwent a biopsy within a clinical trial. To our knowledge, there are no results of mpMRI and/or biopsies in the setting after both radiotherapy and focal salvage HIFU in the literature.

5.1.5.4 Clinical Implications

Furthermore, because of the broader patient selection in the present study (including patients with seminal vesicle involvement), more extensive disease was potentially treated, thereby increasing the risk of side effects. Only comparative studies, however, would provide a robust estimate of side effects of different salvage techniques.

5.1.5.5 Future Research

It is quite clear that prospective studies are required. The Focal Recurrent Assessment and Salvage Treatment for Radiorecurrent Prostate Cancer (FORECAST) study (113) will examine focal salvage cryotherapy and HIFU as well as the role of imaging in excluding metastatic disease and diagnosing local recurrence. We are also planning comparative studies, although accrual of patients is often difficult (114).

5.1.6 Conclusion

In conclusion, focal salvage HIFU confers relatively low complication and side effect rates. CEFS and biochemical control in the short to medium term is reasonable, especially in this relatively high-risk cohort, but still on the low side compared with current whole-gland salvage therapies. Focal salvage therapy may offer disease control in patients at high risk, whilst minimizing additional treatment morbidities.

5.2 Focal Salvage Therapy for radiorecurrent prostate cancer

5.2.1 Introduction

Throughout this discussion, it has been made clear the necessity to treat men with radiorecurrent prostate cancer with a modality that offers the least morbidity and mortality with optimum cancer control. Focal salvage therapy using either HIFU or cryotherapy may be suitable options. In order to provide focal salvage therapy, disease must be localized accurately to ensure high grade disease is not left untreated which could lead to further disease progression. We now report on the prospective outcomes of focal salvage HIFU (FS-HIFU) and cryotherapy (FS-cryotherapy) from the FORECAST study.

5.2.2 Methods and Materials

As described above in Chapter 3.2 WB-MRI vs. Choline PET/CT and bone scan in detection of radiorecurrent disease:

Patient selection

Eligibility criteria for the trial primarily include men who biochemical failure after having had previous external beam radiotherapy or brachytherapy with or without neo-adjuvant/adjuvant hormone therapy. Biochemical failure as defined by the Phoenix criteria (PSA nadir + 2 ng/ml).

See Appendix 10.1 for protocol with full inclusion and exclusion criteria.

Imaging

All patients underwent Choline PET/CT-CT, radio-isotope bone-scan (if not already carried out in the last 6 months, mpMRI Pelvis/prostate and whole-body MRI (See above Flowchart 1 – FORECAST Study). If these

investigations revealed metastatic disease they were withdrawn from the trial. Patients then underwent TPM biopsy (see Chapter 4.1 Targeted transperineal prostate biopsy in the detection of radiorecurrent prostate cancer) using a modified version of that described by Barzell et al. (74). (See Figure 1 - Transperineal Prostate Mapping Modified Barzell Zones above- Chapter 4.1 Targeted transperineal prostate biopsy in the detection of radiorecurrent prostate cancer). If mpMRI prior to biopsy identified a visible lesion, MRI cognitive targeted sampling were taken by comparing the pre-intervention mpMRI to the live intra-operative prostate ultrasound on two different screens (cognitive or visually targeted).

Following biopsy, results were reviewed in MDT alongside imaging to determine suitability for focal salvage treatment.

Focal Salvage Treatment

As described above in Chapter 2 – Hypotheses - Focal salvage treatment could be provided if:

- Disease was confined to a quadrant of the prostate provided that less than one half of the lobe is affected.

- At least one neurovascular bundle was avoided by ensuring a minimum distance of ablation zone to contralateral neurovascular bundle of 10 mm.

- In men in whom both lobes met criteria for clinically insignificant cancer (≤3 mm and absence of Gleason pattern 4), the lobe with the dominant disease burden was treated.

If there is identical bilateral disease burden, the side with the highest score for probability of malignancy on mpMRI will be treated. If this is also equivalent, a second re-view of the biopsies will be requested by the trial pathologist and the dominant side treated. Only those patients with exactly equivalent disease

bilaterally following these three reviews will be excluded from the trial. See Appendix 10.1 Protocol for methods of focal salvage therapy.

Focal salvage treatment was not offered if cancer was seen at the overlapping or going into the apical sphincter on mpMRI.

Treatment methods

The decision between focal cryotherapy or HIFU salvage ablative methods will be based on the location of recurrent disease. Patients were more likely to undergo cryotherapy if the tumour was predominantly anterior and HIFU if the tumour was posterior and/or apical. This is to ensure optimum energy delivery as HIFU can often not deliver energy in the upper parts of the prostate whilst the cryoprobes can be placed directly into the area of the tumour. The decision in those which are basal-middle and posterior will be pragmatically chosen by physician and patient as would happen in standard care.

Follow-up

This took place at 4 weeks, 3 months, 6 months, 9 months and 12 months post-treatment. At each follow-up appointment, the patient had either a telephone consultation or clinic visit to discuss their results and review any adverse events using National Cancer Institute Common Terminology Criteria (NCI CTC) classification system. IPSS, IPSS QoL, UCLA-EPIC Bowel Questionnaire, erectile dysfunction, the IIEF-15 questionnaires were completed during follow up to assess any change in urinary, bowel or sexual function and a PSA blood test. At 12 months, patients had mpMRI to see if there is any evidence of residual disease. If post treatment, there is a PSA doubling time of less than 3 months or fails by PHOENIX/ASTRO Definition (PSA nadir + 2 ng/ml) patients underwent repeat prostate mpMRI and if warranted repeat mpMRI targeted biopsy+/staging scans (Choline PET/CT or Bone Scan).

Patients were excluded from analysis if they are withdrawn from the study or unable to undergo the reference test after one of the index test, or are unable to have focal salvage treatment.

5.2.3 Objectives

5.2.3.1 Primary Objectives

1. To determine the complications and side-effect profile of focal salvage therapy to treat localised radiorecurrent prostate cancer.

2. Presence of urinary incontinence (any pad usage plus any leakage of urine) as determined by the UCLA-EPIC urinary continence questionnaire (See Appendix 10.2), at 12 months, in those men with no urinary incontinence at baseline.

3. Assess further functional outcomes using validated questionnaires.

   The IPSS – International Prostate Symptom score - comprises of 8 questions in total, 7 on urinary function and 1 on Quality of Life (QOL) (See Appendix 10.2). Scoring is as follows; Mild lower urinary tract symptoms (LUTS) (symptom score less than or equal to 7), Moderate LUTS (symptom score range 8-19) and Severe LUTS (symptom score range 20-35).

   The 15-question International Index of Erectile Function (IIEF) Questionnaire. is a validated, multidimensional, self-administered investigation that assesses erectile dysfunction and has been used to assess treatment outcomes in clinical trials. A score of 0-5 is awarded to each of the 15 questions that examine the 4 main domains of male sexual function: erectile function, orgasmic function, sexual desire and intercourse satisfaction. (121). Maximum score is 75 with higher scores

indicating good sexual function.(See appendix 10.2) Specific questions that were analysed for this study were erectile functional questions specifically looking at patients were able to satisfactorily obtain and maintain an erection sufficient for sexual intercourse.
Other questionnaires used to examine urinary and bowel function post treatment are University of California-Los Angeles - Expanded Prostate Index Composite (EPIC) which examines Quality of Life issues in patients with Prostate cancer (120,129) . These questions examined urinary and bowel urgency (A low score indicated poor control <12), leakage (low score indicated poor control <12), and the use of any pads (high score >2 indicated increased pad usage). Quality of life was also assessed in these questionnaires (scores >15 indicated poor quality of life).

5.2.3.2 Secondary Objectives

To provide preliminary data on short term disease control outcomes after one or two focal salvage therapy (PSA kinetics, imaging evidence of localised recurrence, rate of ADT and metastases/death). BCF using the Phoenix-ASTRO definition (nadir PSA + 2 ng/mL) after FST, and a composite failure that consisted of failing by one of the following parameters; BCF and/or positive localized or distant imaging and/or positive biopsy and/or systemic therapy and/or metastases and/or prostate cancer-specific death, was also calculated.

Statistical Analysis

Cox proportional hazards regression was used to quantify the effect of the determinants described above on the endpoints. Hazard ratios (HRs) with 95% CIs are provided. Factors with *P* values <0.05 were included in the multivariable model. The R language environment (version 3.2.1; available at http://www.r-project.org/) (122) was used for all statistical analyses.

5.2.4 Results

A total of 19 patients have undergone focal salvage therapy so far between June 2014 and September 2015. Of these, 21.1% (4/19), 15.8% (3/19) and 52.6% (10/19) had low-, intermediate- and high-risk disease prior to radiotherapy (10.5% 2/19 missing). A total of 94.7% (18/19) of the patients underwent EBRT and 5.3% (1/19) underwent brachytherapy. The median time to BCF from primary radiotherapy was 89.5 months (95% CI 53.2-88.5). The mean (SD) age at focal salvage therapy was 68.7 (8.2) years and the median (interquartile range [IQR]) PSA level before focal salvage treatment was 5.6 ng/mL (2.5-7.7). (See Table 48 – Baseline Data)

Table 48 - Baseline Characteristics

Baseline Characteristics (N=19)		
Determinant	Mean/median/n (SD, IQR, %)	Missing, n (%)
Patient age	68.7 (8.2)	0 (0%)
D'Amico Risk at Baseline prior to radiotherapy 1 = Low risk T1-T2b GG <6 PSA <10 2 = Intermediate risk T2b and/or GG 7 and or PSA 10-20 3 = High risk >T2c and/or Gleason 8-10 and/or PSA >20	 4 (21.1%) 3 (15.8%) 10 (52.6%)	 2 (10.5%)
Nadir PSA post-treatment	0.13 (0.10-0.53)	1 (5%)
Referral PSA	4.6 (2.5-5.8)	0 (0%)
SD=standard deviation; IQR=interquartile range; BF=biochemical failure; EBRT=external beam radiotherapy; Gy=Gray; PSA=prostate specific antigen.		

15 patients underwent FS-HIFU and 4 patients underwent FS-cryotherapy. Forms of ablation performed consisted of quadrant 63.1%(12/19), hemiablation 15.8% (3/19), dog-leg ablation 15.8% (3/19) and subtotal ablation 5.3% (1/19) forms of ablation were performed. 89.5% (17/19) patients had whole area of disease recurrence treated and 10.5% (2/19) had Index lesion ablation. In the patients who had index lesion ablation, remaining untreated disease consisted of Gleason 3+3 MCCL 7.5mm in midline in one patient and another had Gleason 3+4 MCCL 5mm on same side.

5.2.4.1 Primary Objective Outcomes

5.2.4.1.1 Side effects

Side effects directly related to focal salvage treatment included persistent debris post operatively (n=1), straining to pass urine (n=1) and urethral soreness (n=1). Other medical complaints post operatively included lightheadiness due to tamsulosin use (n=1), development of glaucoma (n=1) and neck pain (n=1). The patient who had debris postoperatively, later developed urethral stricture and underwent urethral dilation one year after treatment. The patient who was straining to pass urine, developed perineal pain and this is currently being conservatively managed.

Only 2 patients underwent repeat MRI due to rising PSA within 12 months of treatment. Both of whom scored PIRADS 4 (clinically significant cancer is likely to be present). One of these patients underwent biopsy post FST due to MRI findings. Biopsy revealed Gleason 3+4 MCCL 5mm on same side of initial salvage treatment and he went on to have a further FST with FS-Cryotherapy. The remaining patient was started on hormonal therapy as Choline PET/CT revealed nodal disease. One patient who developed nodal metastases 10 months after FST received cyberknife to these metastases.

5.2.4.1.2 Urinary Leakage

All patients still had urinary control without leakage at 12 months post FST. No patient reported pad use at baseline or 12 months post FST.

5.2.4.1.3 Functional Outcomes

Using paired t test baseline and functional scores were assessed at 4 weeks, 3 months, 6 months and 12 months post focal salvage treatment. For this discussion, functional outcomes at 12 months only will be discussed. These are shown in Table 49. (For full outcomes please see Appendix 10.3)

Table 49 – Functional outcomes– Baseline scores of functional questionnaires and 12 months.

	Mean	Median	SD
Baseline IPSS (n=18)	9.67	8.00	5.531
Baseline IPSS QOL	1.44	1.00	1.247
Baseline IIEF-15 (n=18)	21.61	15.00	19.162
Baseline IIEF -1	1.978	.50	1.50
Baseline IIEF-2	1.33	.00	1.910
Baseline IIEF-3	1.17	.00	1.886
Baseline IIEF-4	1.06	.00	1.862
Baseline IIEF – 5 (n=16)	1.69	1.00	1.352
Baseline UCLA EPIC URINE (n=17)	23.53	23.00	3.145
Baseline UCLA EPIC URINE 1	4.65	5.00	.862
Baseline UCLA EPIC URINE 4	3.76	4.00	.437
Baseline UCLA EPIC URINE 5	.00	.00	.000
Baseline UCLA EPIC BOWEL (n=18)	24.17	23.00	3.808
Baseline UCLA EPIC BOWEL 1	4.72	5.00	.752
Baseline UCLA EPIC BOWEL 2	5.00	5.00	.000

Baseline UCLA EPIC BOWEL 8D	.22	.00	.428
12 MTH IPSS (N=8)	11.88	11.50	6.379
12 MTH IPSS QOL	2.13	2.50	1.126
12 MTH IIEF-15	15.63	13.50	7.999
12 MTH IIEF -1	.50	.00	.756
12 MTH IIEF-2	.38	.00	.518
12 MTH IIEF-3	.25	.00	.707
12 MTH IIEF-4	.13	.00	.354
12 MTH IIEF - 5	1.13	1.00	.354
12 MTH UCLA EPIC URINE	26.13	25.00	3.944
12 MTH UCLA EPIC URINE 1	4.63	5.00	.518
12 MTH UCLA EPIC URINE 4	3.50	3.50	.535
12 MTH UCLA EPIC URINE 5	.00	.00	.000
12 MTH UCLA EPIC BOWEL	25.63	24.50	6.501
12 MTH UCLA EPIC BOWEL 1	4.75	5.00	.463
12 MTH UCLA EPIC BOWEL 2	4.88	5.00	.354
12 MTH UCLA EPIC BOWEL 8D	.50	.00	.756

Baseline overall IPSS score was 11.38 and at 12 months was 11.88 (p=0.83). IPSS QOL scores at baseline and 12 months was 1.50 and 2.13 respectively (p=0.14). Baseline IIEF-1 which asks how often patients get an erection during sexual activity, baseline score was 1.38 and at 12 months this was 0.50 (p = 0.11). Baseline IIEF-2 score was 1.25 and 0.38 at 12 months (p=0.18). Baseline IIEF-3 score at baseline and 12 months was 1.00 and 0.25 (p=0.17). Baseline IIEF-4 scores was 0.88 and 0.13 at 12 months (p=0.20). Baseline IIEF-5 score was 1.57 and 1.14 at 12 months (p=0.20). Baseline EPIC – Urine score 1 was 4.88 and at 12 months was 4.63 (p=0.17). Baseline EPIC – Urine score 4 was 3.88 and 3.50 at 12 months(p=0.20). UCLA –EPIC Bowel 1 was 5.00 and 4.75 at 12 months (p=0.17). UCLA –EPIC Bowel 2 was 5.00 and 4.88 at 12 months (p=0.35). Baseline EPIC Bowel 8D – was 0.00 and 0.50 at 12 months (p=0.10). For further outcomes please see Table 50 – Paired t –test Functional outcomes – in Section 10.3.2)

5.2.4.2 Secondary objectives

5.2.4.2.1 Biochemical Failure

b-DFS at 6 months for the entire group, was 95% (95% CI 86-100) and at 12 months, was 75% (95% CI 56-100). (See Figure 8) All patients who achieved a PSA nadir of <0.5ng/ml had b-DFS rate of 100% at 6 and 12 months (p=0.02). For those who achieved a PSA nadir of >0.5ng/ml b-DFS rates were 90% (95% CI 73-100) at 6 months and 46% (95% CI 21-100) at 12 months (p=0.02) (See Figure 9). Patients who underwent focal salvage HIFU had a b-DFS rate of 93% (95% CI 80-100) at 6 months, and 73% (95% CI 51-100) at 12 months (p=0.95). For patients who underwent focal salvage cryotherapy, b-DFS rates at 6 months and 12 months were 100% and 67% (95% CI 30-100) respectively (p=0.95) (See Figure 10).

Figure 8 Biochemical Disease Free Survival – Entire Group

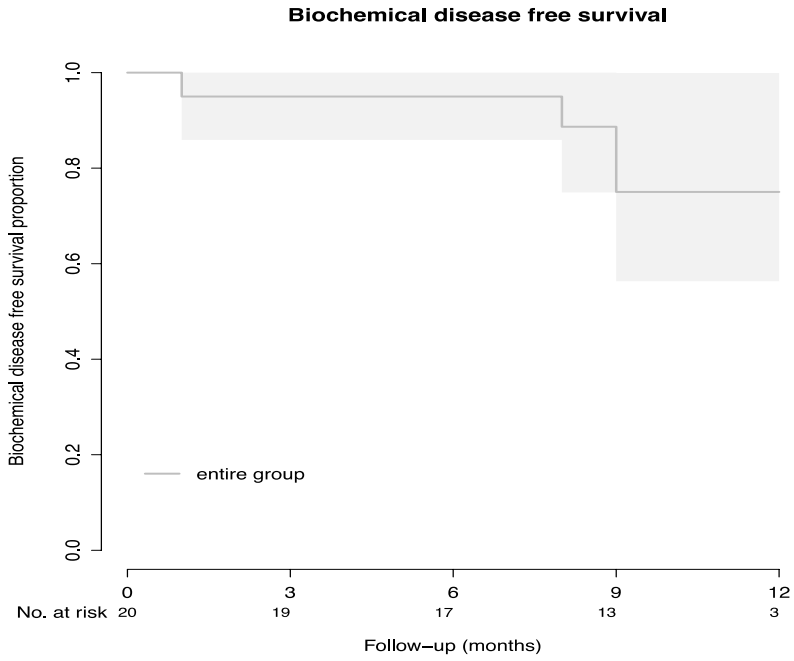


Figure 9 Biochemical Disease Free Survival according to PSA Nadir Failure

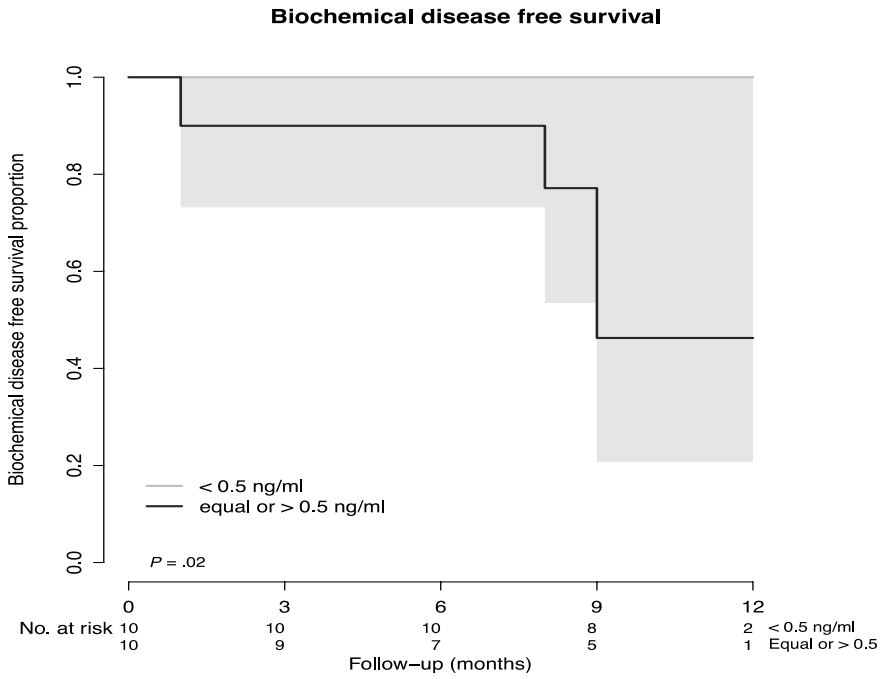
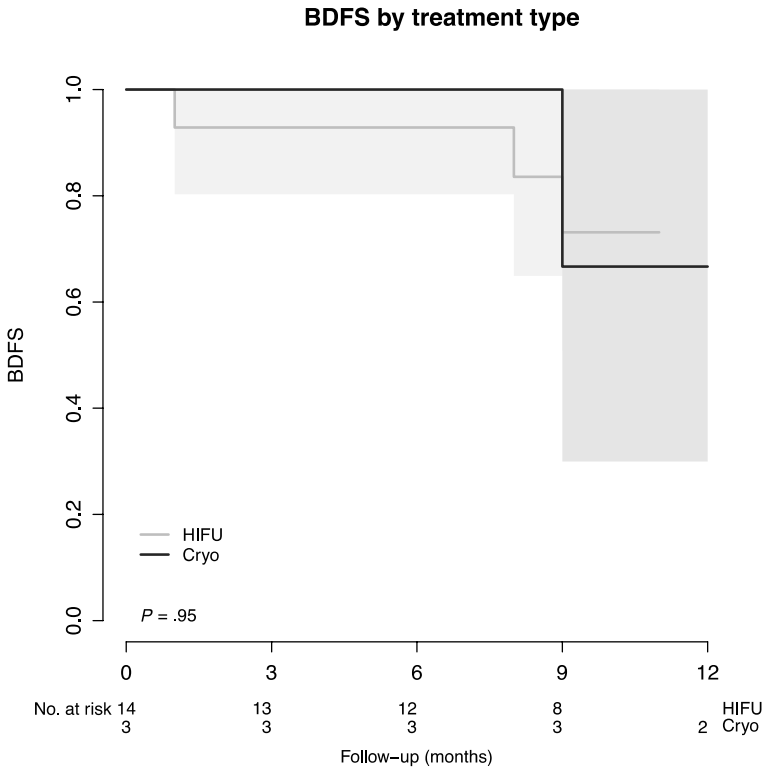


Figure 10 Biochemical Disease Free Survival according to Focal Salvage Treatment Type



5.2.4.2.2 Composite Endpoint

Composite endpoint free survival (CEFS) for the entire group, was 85% (95% CI 71-100) at 6 months and 18% (7-51%) at 12 months. All patients who achieved a PSA nadir of <0.5ng/ml had CEFS rate of 100% at 6 months and but at 12 months this was only 11% (95% CI 2-71). For those who achieved a PSA nadir of ≥0.5ng/ml and CEFS rates of 70% (95% CI 47-100) at 6 months and 28% (95% CI 9-88) at 12 months (p=0.37). Patients who underwent focal salvage HIFU had a CEFS rate of 86% (95% CI 69-100) at 6 months, and 8% (95% CI 1-51) at 12 months. For patients who underwent focal salvage cryotherapy, CEFS rates at 6 months and 12 months were 75% (95% CI 43-100) and 0% respectively (p=0.41) (See Figures 11-13).

Figure 11 - Composite endpoint free survival (CEFS) for the entire group

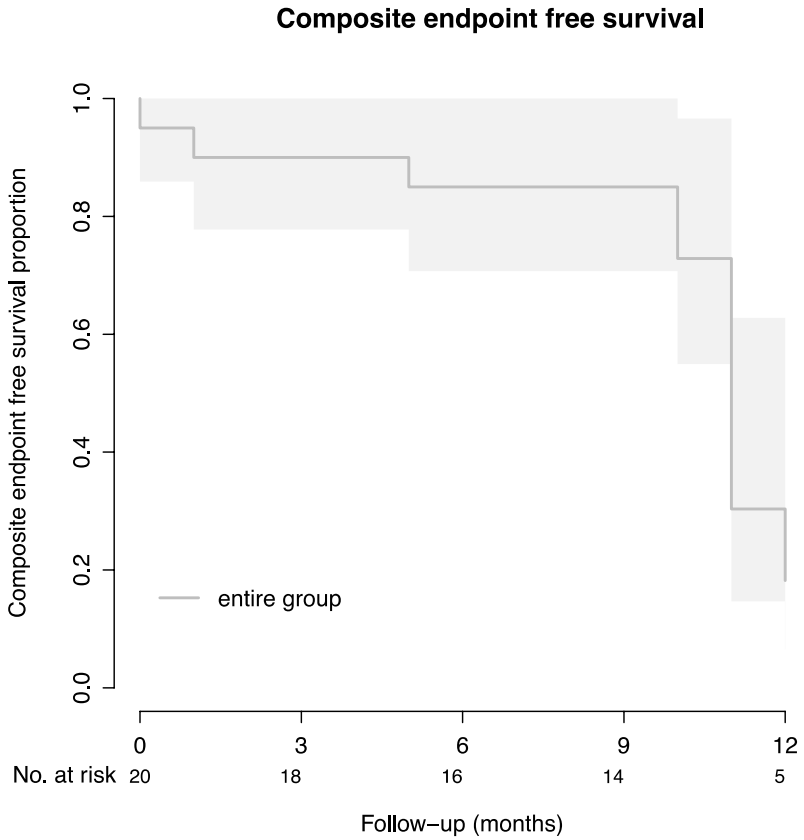


Figure 12 - Composite endpoint free survival according to PSA nadir

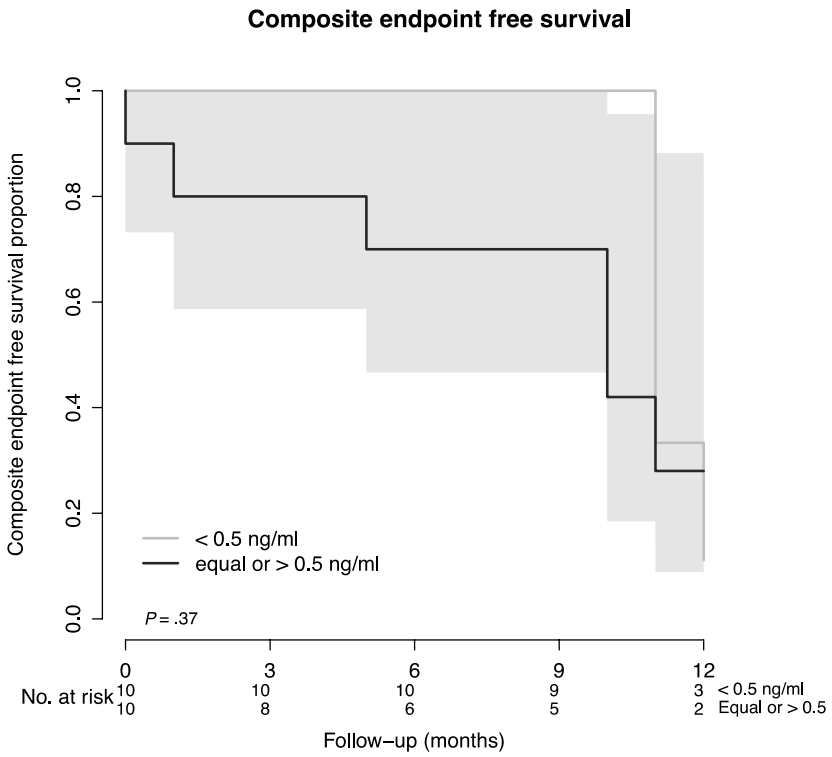
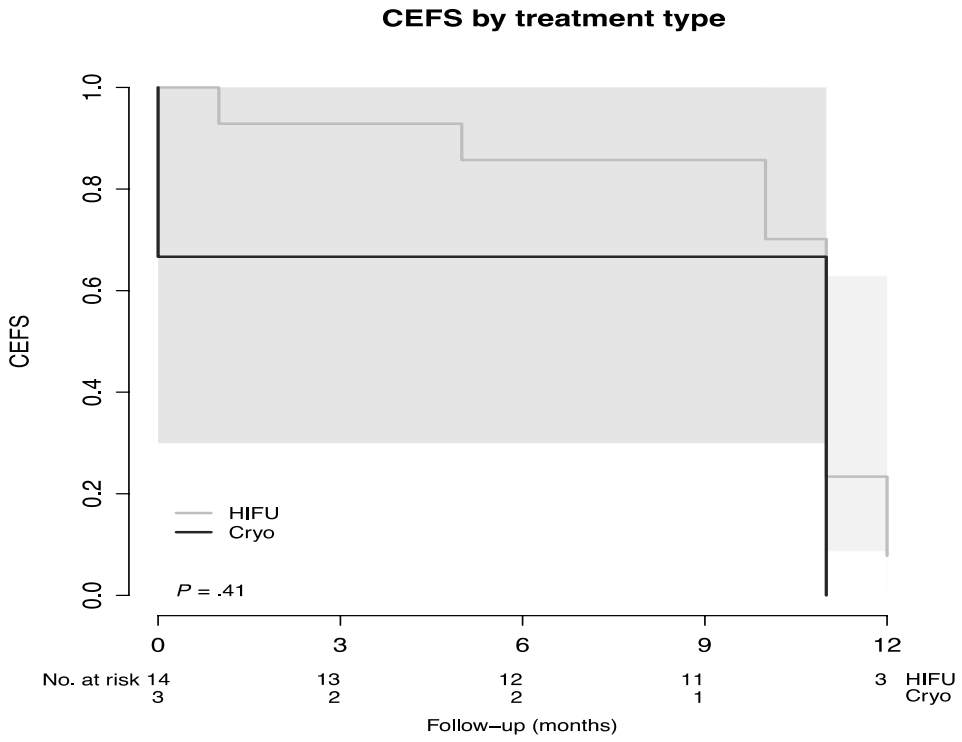


Figure 13 - Composite endpoint free survival according to Focal Salvage treatment type



5.2.5 Discussion

5.2.5.1 Summary of results

Our study has shown the potential of focal salvage HIFU and cryotherapy as a salvage treatment post radiotherapy. b-DFS rates post FS-HIFU was 93% (95% CI 80-100) at 6 months, and 73% (95% CI 51-100) at 12 months (p=0.95). For focal salvage cryotherapy this was 100% and 67% (95% CI 30-100) respectively (p=0.95). Only one patient developed Clavien 3b complication – urethral stricture requiring dilation - and there are no prostate cancer related deaths at present.

5.2.5.2 Methodological Limitations

The key limitation to this current study, is our small study population. As a result, it was not possible to perform univariable and multivariable analysis for factors predicting biochemical failure or failure by composite endpoint. Our small sample size also hindered analysis between focal salvage treatments i.e. comparing functional and cancer control outcomes between focal salvage HIFU and focal salvage cryotherapy.

5.2.5.3 Comparison to other studies

Our initial outcomes have shown good rates of b-DFS. In comparison to Ahmed et al. (70) which examined focal salvage HIFU in 39 patients, b-DFS rates at one year for the overall group was 69%. For our group who underwent FS-HIFU, (n=15) all patients who achieved a PSA nadir of <0.5ng/ml had b-DFS rate of 100% at 12 months (p=0.02) compared with 86% in Ahmed's group (70). However our b-DFS rates were lower for those who had PSA nadir of 46% vs. 49% respectively at 12 months.

Eisenberg et al. is another small study providing b-DFS rates at one year. In this study 19 men focal salvage cryotherapy (hemi-gland treatment) and had a B-DFS survival rate of 89% at 12 months and 69% at 2 years (69). Only 4 patients in our analysis have undergone FS-cryotherapy therefore whilst our rates of b-DFS do appear to be favourable, further analysis once FORECAST has completed recruitment will likely result in larger numbers being treated with focal salvage cryotherapy providing more robust data for comparison.

In terms of functional outcomes; patients (n=8) had moderate LUTS at baseline which did not significantly change post treatment and this was the same with QOL where patients were mostly satisfied with their LUTS pre-and post FST. Examining successful maintenance of an erection sufficient for intercourse, there was no significant change between baseline and 12-month erectile function. All patients still had urinary control without leakage at 12 months' post FST. No patient reported pad use at baseline or 12 months' post FST. Again, there was no increase in rectal urgency, or leakage of stool post FST at 12 months. There was only a small change in losing control of stool from no problem to very small problem however this was not significant. In comparison to our previous study (130), 32.4% had reported urinary leakage and 12.5% started using pads at 2 years. Bladder neck strictures requiring dilation rates in current literature are 3-8% (12/150) (69,70,130). Currently within this study there are no patients who have suffered from recto-urethral fistula.

5.2.5.4 Clinical implications

Focal salvage treatment in the form of HIFU or cryotherapy appears to have good short to medium term outcomes with minimal morbidity. Ours is the first study to use a composite endpoint - this can be employed in future studies to determine outcomes of salvage treatment.

5.2.5.5 Future research

Upon completion of the FORECAST Study – a larger sample size will provide much needed data on intermediate outcomes for disease control and side effects of focal salvage therapy. This study will also provide information on radiological and histopathological investigations in radiorecurrent disease. This will enable further clinical discussion on how to best investigate biochemical failure post radiotherapy which in turn can help patients towards the most suitable form of salvage treatment.

5.2.6 Conclusion

Focal salvage therapy holds promise in further treatment of radio-recurrent prostate cancer. We have shown no change in baseline function of urinary or bowel symptoms. Whilst our biochemical rates appear favourable, further completion of recruitment to the FORECAST study will provide more data for comparison to current literature.

Chapter 6 Summary and Clinical Implications

Each chapter in this thesis is an attempt to follow a patient's journey from biochemical failure through to diagnosis of radiorecurrent disease and ongoing further salvage treatment. This chapter offers a critical discussion of the studies included in this thesis.

6.1 Choline PET/CT VS. Bone Scan

Current standards of care for staging patients at time of biochemical failure post radiotherapy include Choline PET/CT and bone scan. These scans are limited by their detection of metastases at high levels of PSA (PSA>20ng/ml). However, these scans had to be included in the thesis as they are currently not superseded by another imaging test. The question remains, can only bone scan or Choline PET/CT be used in the diagnosis of distant radiorecurrent disease? Thereby reducing the burden on the patient and saving costs.

In Chapter 3.1 a retrospective study was performed that compared Choline PET/CT to bone scan in the detection of metastatic radiorecurrent disease. 97 patients were examined and Median PSA pre-imaging was 4.80 ng/ml (IQR 2.7-7.3). Average (±SD) time from biochemical failure to bone scan and Choline PET/CT scan was 9 months (±13.2). Bone scan was positive in 3.1% (3/97), equivocal in 15.5% (15/97) and negative in 81.4% (79/95). Choline PET/CT scan was positive for metastatic disease in 5.2% (5/97) and equivocal in 3.1% (3/97). Concordance between bone scan and Choline PET/CT occurred in only 3 cases, (kappa value 0.024). Bone scan was equivocal in 15 cases, in comparison with choline positive metastatic disease specifically (11 cases), concordance was reached in one case, was equivocal in a further case and negative on Choline PET/CT for 9 cases (kappa value 0.14). Choline PET/CT was positive for metastatic bony disease in 5 cases. In one case, Choline PET/CT and bone scan was concordant, in one case bone scan was equivocal and in three cases, bone scan was negative (kappa value 0.14). When bone scan positive and equivocal results were combined (n=14)

and compared with Choline PET/CT, only 2 cases were concordant with one case being equivocal and 11 cases being negative for metastatic disease (kappa value 0.13).

6.1.1 Clinical implications

Throughout the analysis, it was shown that concordance between Choline PET/CT and Bone scan had low kappa scores - (kappa value 0.024 – 0.14) indicating very unlikely to be concordance between these tests. This indicates that neither scan can be replaced with one of the other in the detection of metastatic disease. The key limitations in this paper, is that the PSA value at time of imaging is 4.80 ng/ml (IQR 2.7-7.3). Average (±SD) time from biochemical failure to bone scan and Choline PET/CT scan was 9 months (±13.2). Metastatic disease can declare itself up to 2 years post biochemical failure and more importantly it is widely shown that both imaging tests have higher rates of detection of metastatic disease at higher PSA levels >20ng/ml. This is an issue that is difficult to overcome in this study as salvage treatment is felt to be most beneficial in patients with PSA <20ng/ml. Overall it would still be justified to perform both tests to rule out metastatic disease, as Choline PET/CT was still positive in 23 patients (nodal and metastatic disease) and bone scan was positive (positive and equivocal combined) in up to 18 patients. Ultimately a more accurate imaging test is required to diagnose metastatic disease with at a lower PSA threshold.

6.2 WB-MRI VS Choline PET/CT and Bone Scan

In this study results from the prospective FORECAST trial were analysed. WB-MRI is an innovative technique that can scan the body in 60 minutes without the need for radioactive tracer. This single test may have the ability to replace current standard of care nuclear medicine scans if it is capable of detecting metastatic disease at low PSA levels (PSA <20ng/ml).

In this study, WB-MRI was compared to Choline PET/CT and Bone Scan to diagnose radiorecurrent prostate cancer. Patients were classified as low 6% (5/48), intermediate 30.9% (30/48) and high-risk disease 49.5% (48/48) according to D'Amico classification at baseline prior to external beam radiotherapy (EBRT) (Missing baseline data in 2 cases). The time from EBRT to re-imaging was 78.9 (IQR 48.5-93.8) The median PSA at the time of imaging was 3.29 ng/ml (interquartile range 2.40-5.30).

WB-MRI identified local tumour in 52% (26/50) of cases, nodal disease being positive or equivocal in 6% (3/50) and 26% (13/50) of cases respectively. WB-MRI reported metastatic bony disease as positive in 4% (2/50), equivocal 10% (5/50). Choline PET/CT was positive for local disease in 66% (33/50) of cases, and negative in 28% (14/50), nodal disease in 24% (12/50), tissue metastases in 4% (2/50) and in bony metastatic disease was positive in 6% (3/50) and equivocal 2% (1/50). Bone scan was positive and equivocal in 4% of cases (2/50) respectively.

Concordance between WB-MRI and Choline PET/CT occurred in 20 cases for local disease Kappa score 0.311 ($p=0.056$). Of 19 patients where nodal status was reported kappa score indicating concordance between WB-MRI and Choline PET/CT was up to 0.548 ($p=0.00032$). Concordance between WB-MRI and Choline PET/CT for bony metastatic disease had a kappa score 0.411 ($p<0.0001$). Concordance was achieved in only one case for bone metastatic disease between WB-MRI and Bone scan (kappa score 0.333 $p=0.157$).

Concordance between Choline PET/CT and bone scan was achieved in 2 cases for bony metastatic disease was detected on Choline PET/CT and bone scan. Kappa score = 0.333 ($p=0.46$)).

6.2.1 Clinical implications

Overall there was better concordance between WB-MRI and standard of care tests compared to concordance between standard of care tests. Moderate agreement with a kappa score of 0.548 of WB-MRI and Choline PET/CT for nodal disease is promising. However, it does not appear yet that WB-MRI can replace Choline PET/CT for identification of local disease as kappa score was again only fair at 0.311 nor can WB-MRI replace bone scan for identification of bony lesions **(**kappa score of 0.333).

Several limitations of this study include low PSA at time of imaging, (median PSA at the time of imaging was 3.29 ng/ml (interquartile range 2.40-5.30), low patient numbers (n=50) and no histopathological confirmation of local, nodal or bony metastatic disease. For local disease however, it may be possible in the future to examine TPM outcomes of patients who proceed to biopsy and then examine which of three imaging test – WB-MRI, Choline PET/CT and pelvic mpMRI – has the greatest sensitivity and specificity in identifying local disease. Scans may have to be re-reviewed to perform this analysis, so that a per quadrant based report of the prostate, is fulfilled for each scan. This can then be confirmed with histopathological results of TPM biopsy.

Currently we have been unable to support whether WB-MRI has greater sensitivity for the detection of metastases in radio-recurrent disease compared to standard of care tests. This is in part to not having histopathological conformation, but also to the fact that there were limited number of bony lesions found (7/50 in total for all imaging) and repeat imaging post treatment/end of follow up is yet to be performed. Further analyses to determine accuracy of WB-MRI will be to determine the persistence of lesions post salvage treatment. This will be reported in the final outcomes of the FORECAST Study.

6.3 Targeted transperineal prostate biopsy in the detection of radiorecurrent prostate cancer

mpMRI has gained acceptance in the diagnosis of localised prostate cancer. The aim of this retrospective study was to examine biopsies targeted to a MRI lesion compared with whole gland TPM sampling to determine which of the techniques had the higher accuracy. Clinically significant cancer was defined using University College London (UCL)/Ahmed definition 2 (Gleason ≥3+4 and/or maximum cancer core length (MCCL) ≥4 mm). 77 patients were included and median PSA was 4.68ng/ml (0.54-20; IQR 2.68-7.60). TPM had a better detection rate of clinically significant cancer compared with MRI-TB 85.7% vs. 77.9% respectively.

On a per core analysis MRI-TB was more efficient as 50% of MRI-TB cores were positive for clinically significant cancer compared with 17.8% of TPM cores. MRI-TB had a similar rate of detection of UCL/Ahmed definition 1 disease compared with TPM 68% versus 71%. TPM had a higher detection rate of Gleason 3+4 cancer compared with MRI-TB 84.4% versus 75.3%. TPM had a higher all cancer detection rate of 89.6% compared with 63 patients 81.8% for MRI-TB.

6.3.1 Clinical Implications

Overall TPM biopsy was better at detecting clinically significant prostate cancer compared to MRI-TB. As a result, it would not be advised that only MRI-TB should be performed. In order to improve the accuracy of MRI-TB several strategies can be considered such as US-Fusion biopsies that conform pre-operative MRI to live US images of the prostate. This allows for changes in the gland due to patient position. Another possibility is live MRI targeting, however this would require a dedicated unit with specialized equipment and trained staff. Cases may also take longer, meaning that operating lists are less efficient as fewer patients can be biopsies on one list compared to current TPM biopsy lists. This study did show that TPM biopsy had a 90% detection rate of clinically significant cancer with PIRADS score ≥

4 and MRI-TB had a detection rate of 85.1%. This is reassuring and does support the hypothesis that abnormalities seen with mpMRI are associated with clinically significant prostate cancer in the radio-recurrent prostate cancer setting.

6.4 Multiparametric MRI in detection of radiorecurrent disease

Accurate localization of radiorecurrent disease is paramount in providing focal salvage therapy. Multi-parametric MRI (MpMRI) has been shown to have promise in the diagnosis of radiorecurrent disease as discussed above. The detection rate of mpMRI within the FORECAST Study was examined using Likert Score as described above - (1, highly likely no tumour; 5, highly likely tumour) (96). TPM biopsy was used as the reference test.

Data was available for 36 patients who underwent mpMRI as part of the FORECAST Trial. Metastatic disease had been ruled out prior to mpMRI by bone scan and Choline PET/CT. Overall mpMRI PIRADS ≥4 was shown to have high sensitivity, specificity, PPV and NPV for detection of UCL definition 1 and 2 disease 89.5%, 76.5%, 81% and 86.8% AUROC was 0.83 (SE 0.074 p=0.001) and 90%, 81.3%, 85.7% and 86.7% (AUROC) was 0.856 (SE 0.07 p=0.000)) respectively. For detection of any cancer this was 85.7%, 80%, 85.7% and 80% respectively (p=0.00), (AUROC) was 0.829 (SE 0.075 p=0.01).

For detection of clinically significant cancer as defined by UCL Definition 2 MRI PIRADS Score ≥3, Sensitivity, specificity, PPV and NPV was 87.5%, 80.0%, 82.4% and 85.7% respectively and AUROC was 0.563 (SE 0.1 p=0.52). For detection of UCL Definition 1 disease, this was 86.7%, 75.0%, 76.5% and 85.7% (AUROC) was 0.559 (SE 0.098 p=0.55). Sensitivity, specificity, PPV and NPV of MRI to detect any cancer was 82.4%, 78.6%, 82.4% and 78.6% AUROC was 0.567 (SE 0.1 p=0.5).

Whilst TPM biopsy and MRI-TB were concordant in most cases, for detection of clinically significant cancer for both UCL Definition 1 & 2 disease, however, MRI-TB misclassified up to 6 patients as having no cancer, when clinically significant cancer was present on TPM biopsy.

6.4.1 Clinical Implications

mpMRI shows high accuracy in the detection of clinically significant radiorecurrent prostate cancer. Whilst PIRADS Score ≥4 shows high accuracy rates PIRADS ≥ 3 had a lower specificity and AUROC. This would suggest that all PIRADS 3 lesions should be biopsied. This study still showed that TPM biopsy outperformed MRI-TB and therefore we would not advocate that sole MRI-TB can replace TPM at present.

6.5 Radiorecurrent prostate cancer features on template biopsy: Implications for focal salvage therapy

In this chapter, we sought to evaluate the proportion of men presenting with presumed localized radiorecurrent prostate cancer who might be suitable for FST based on TPM biopsies.

A retrospective study on 145 men was performed. All patients had undergone metastatic screening to ensure no presence of metastatic disease. Median PSA at imaging and subsequent biopsy 4.5ng/ml (2.5-7.7). 60% of patients were found to be suitable for a form of focal salvage therapy. 40.7% (59/145) were suitable for quadrant ablation, 14.5% (21/145) for hemiablation, 14.5% (21/145) for bilateral lesion ablation and 6.2% (9/145) for index lesion ablation. Only 9.0% (13/145) would require whole-gland treatment only. 15.9% (22/145) did not have any local recurrent disease and were deemed to have likely micrometastatic disease not visible on imaging. Of patients found to have high risk cancer -UCL Definition 1 cancer (Gleason >/=4+3 OR any grade of cancer length >/=6mm)- 14% required whole gland ablation, whilst the remainder were suitable for a form of focal salvage treatment (p=0.004

Pearson χ^2). Both patients classified as low and intermediate risk (UCL Definition 2 or less), could have a form of focal therapy and did not require whole gland treatment.

Patients classified as high risk had a higher odds ratio compared to those of low and intermediate risk of requiring whole gland therapy (odds ratio 5.85 [95% CI 2.13-20.67, p=0.002] and 4.03 [1.18-16.81 p=0.035]), respectively.

6.5.1 Clinical Implications

Patients found to have high risk cancer post radiotherapy are more likely to require whole gland ablation, however our study shows that only 14% will require whole gland treatment, whilst the remainder could be managed with a form of focal therapy. It is still important to note that a definition for clinically significant cancer post radiotherapy has not been defined and therefore the definitions used in this study may still result in a different outcome for those higher risk patients.

Our study is valuable in adding to the literature to determine a definition for clinically significant radiorecurrent cancer as in our univariate analysis showed that total number of positive cores and maximum cancer core length had an odds ratio of 1.14 (95% CI 1.07-1.22, p=<0.0001) and 1.21 (95% CI 1.09-1.34, p=0.0002), respectively, of predicting suitability for whole-gland salvage treatment. This is vital in determining a threshold of Gleason grade, MCCL and potentially number of cores into classifying patients post radiotherapy into low, intermediate and high risk. Ultimately there must be a consensus on these classifications as this will best direct patients towards the most suitable salvage treatment.

6.6 Focal Salvage HIFU

Focal salvage treatment has been shown to carry lower side effects than whole gland salvage treatments. HIFU has the ability of providing focal

treatment to an area of localised prostate cancer. The aim of this retrospective study was to determine composite failure as defined by BCF and/or positive localized or distant imaging and/or positive biopsy and/or systemic therapy and/or metastases and/or prostate cancer-specific death, was also calculated.

A total of 150 patients underwent focal salvage HIFU. Median (interquartile range [IQR]) PSA level before focal salvage treatment was 5.5 (3.6–7.9) ng/mL. Prior to focal salvage HIFU, metastatic disease was excluded by bone scan or Choline PET/CT/FDG scan. Low-, intermediate- and high-risk disease using D'Amico classification, was present in 2.7% (4/150), 39.3% (59/150) and 41.3% (62/150) of patients prior to focal salvage HIFU (missing, *n* = 25 [16.7%]). Three forms of ablation were performed: focal ablation (55%; 82/150); hemi-ablation (34%; 51/150); and index lesion ablation (11%; 17/150).

Composite failure occurred in 61% of patients (91/150). The Kaplan–Meier composite endpoint free survival (CEFS) rate at 3 years was 40% (95% CI 31–50) for the entire group. Kaplan–Meier estimates of CEFS were 100%, 49% and 24% at 3 years in the low-, intermediate- and high-risk groups, respectively, before salvage therapy. When assessing CEFS in PSA responders (post-treatment PSA level ≤0.5 ng/mL) alone, the estimated CEFS rate at 36 months was 67% (95% CI 53–82). A total of 51% of patients (77/150) experienced BCF. The Kaplan–Meier biochemical disease-free survival (b-DFS) rate at 3 years was 48% (95% CI 39–59) for the entire group. Kaplan–Meier estimates of b-DFS were 100%, 61% and 32% at 3 years in the low-, intermediate- and high-risk groups, respectively, before salvage therapy. When assessing BCF in PSA responders alone (PSA nadir ≤0.5 ng/mL), BCF occurred in 12% of patients (18/150) and the estimated actuarial b-DFS rate at 36 months was 78% (95% CI 67–92). The b-DFS rate at 2 years in patients who underwent re-do HIFU, was 66% (95% CI 43–100%).

Complications included UTI in 11.3% of patients (17/150), epididymitis in 1.3% (2/150), bladder neck strictures in 8% (12/150), rectourethral fistula after first HIFU in 2% (3/150) and osteitis pubis in 0.7% (1/150).

In patients with available data from pre- and post-HIFU functional validated questionnaires (UCLA-EPIC, IPSS and IIEF-5), of those pad-free at baseline, 87.5% (42/48) remained pad-free at 2 years. A total of 70.8% (34/48) had drip-free urinary continence at baseline and 67.6% (23/34) remained drip-free postoperatively at 2 years. Baseline IIEF scores were available for 31 patients: 38.1% (12/31) reported a baseline score >2 for question 2 of the IIEF, which meant that erections were mostly sufficient for penetration, and 58.3% (7/12) still had score of >2 at follow-up.

6.6.1 Clinical Implications

Overall Focal Salvage HIFU is a well-tolerated salvage treatment with low rates of significant complication. The hypotheses that the conduct of focal salvage therapy in men with radiorecurrent prostate cancer is both feasible and acceptable can be supported. From this study, patients most likely to benefit from FS-HIFU, are those of low and intermediate risk as these carry the highest b-DFS rate at 3 years (100% and 66% respectively).

Ours is the first study to incorporate all methods of failure and not just biochemical failure post salvage treatment. Using this composite endpoint, low risk groups again had CEFS of 100% at 3 years although those at intermediate risk had a poorer CEFS rate (48%) rate. A composite failure rate could be examined in other studies to report on the success of salvage treatments. Our multivariable analysis showed that higher Gleason Score, T stage 3 and High risk D'Amico pre-salvage were factors in predicting failure by composite endpoint (HR 1.88 [95% CI 1.06–3.32]; P = 0.03), (HR 1.70 [95% CI 1.09–2.65]; and (HR 2.57 [95% CI 0.89–7.38]; P = 0.08)) respectively. These are all factors that can be analysed in future studies to determine whether these too are risk factors for failure post salvage treatment. This is important as currently risk groups are still classified according to D'Amico risk which is prior to radiotherapy. Prediction models can then be made that classify patients into low, intermediate and high risk to determine those most suitable for focal salvage treatment.

6.7 Focal Salvage Treatments

In this chapter, focal salvage HIFU and cryotherapy as part of the prospective FORECAST trial were examined. The main objectives were to report on functional outcomes, biochemical failure rates and composite failure rates as described above.

A total of 19 patients were examined of which 21.1% (4/19), 15.8% (3/19) and 52.6% (10/19) had low-, intermediate- and high-risk disease prior to radiotherapy (10.5% 2/19 missing). The median (interquartile range [IQR]) PSA level before focal salvage treatment was 5.6 ng/mL (2.5-7.7). 15 patients underwent FS-HIFU and 4 patients underwent FS-cryotherapy. Forms of ablation performed consisted of quadrant 63.1%(12/19), hemiablation 15.8% (3/19), dog-leg ablation 15.8% (3/19) and subtotal ablation 5.3% (1/19) Side effects directly related to focal salvage treatment included persistent debris post operatively (n=1), straining to pass urine (n=1) and urethral soreness (n=1). Baseline overall IPSS score was 11.38 and at 12 months was 11.88 (p=0.83). IPSS QOL scores at baseline and 12 months was 1.50 and 2.13 respectively (p=0.14).

b-DFS at 6 months for the entire group, was 95% (95% CI 86-100) and at 12 months, was 75% (95% CI 56-100). Patients who underwent focal salvage HIFU had a b-DFS rate of 93% (95% CI 80-100) at 6 months, and 73% (95% CI 51-100) at 12 months (p=0.95). For patients who underwent focal salvage cryotherapy, b-DFS rates at 6 months and 12 months were 100% and 67% (95% CI 30-100) respectively (p=0.95).

Composite endpoint free survival (CEFS) for the entire group, was 85% (95% CI 71-100) at 6 months and 18% (7-51%) at 12 months. Patients who underwent focal salvage HIFU had a CEFS rate of 86% (95% CI 69-100) at 6 months, and 8% (95% CI 1-51) at 12 months. For patients who underwent focal salvage cryotherapy, CEFS rates at 6 months and 12 months were 75% (95% CI 43-100) and 0% respectively (p=0.41).

6.7.1 Clinical Implications

This study shows that Focal Salvage HIFU and cryotherapy are feasible methods of salvage treatment in radiorecurrent disease with acceptable side effects and with good short term biochemical disease control. In terms of functional outcomes; patients with moderate LUTS at baseline are unlikely to have significant impact on their symptoms post treatment. Men who were potent pre-salvage treatment maintained their potency at 12 months. No new urinary or faecal incontinence was reported. These results however must be interpreted with caution. Importantly, this study had very low numbers with currently very short follow up – 12 months. Also, direct comparison of focal salvage HIFU to cryotherapy could not be examined. By the end of the FORECAST study – the outcomes of each type of therapy will be reported and compared. With a larger patient population and longer follow up more accurate results of how these treatments fare as a curative option for radiorecurrent disease will be seen.

Chapter 7 Main Conclusions

The hypotheses of this thesis were:

1) Whole body MRI has a greater sensitivity for the detection of metastases in patients with radio-recurrent prostate cancer compared to Choline PET/CT and bone scan.

2) Abnormalities seen with multi-parametric MRI are associated with clinically significant prostate cancer in the radio-recurrent prostate cancer setting.

3) The conduct of focal salvage therapy in men with radiorecurrent prostate cancer is both feasible and acceptable.

Based on the results of the studies discussed the following conclusions can be drawn:

Study 3.2 Whole body - MRI vs. Choline PET/CT and Bone Scan in detection of radio-recurrent prostate Cancer

Whole-body MRI can locate nodal metastatic disease however cannot yet replace bone scan in the detection of bony metastatic lesions. There are limitations to calculating the sensitivity of WB-MRI disease as discussed above. Therefore, at present we are unable to confirm or reject Hypotheses 1. However, at the completion of The FORECAST Trial, we will be able to provide results on the accuracy of WB-MRI in the detection of radiorecurrent disease.

Chapter 4.2 Multiparametric MRI in detection of radiorecurrent disease

mpMRI PIRADS 4 showed high accuracy in the detection of clinically significant (UCL Definition 2 (Gleason =3+4 OR any grade of cancer length 4-5mm)) radiorecurrent prostate cancer. This study therefore did support the

hypothesis that abnormalities seen with multi-parametric MRI are associated with clinically significant prostate cancer (using UCL definition) in the radio-recurrent prostate cancer setting.

Chapter 5.1 Focal Salvage HIFU and Chapter 5.2 Focal Salvage treatments

Both of our studies did show that the conduct of focal salvage therapy in men with radiorecurrent prostate cancer is both feasible and has acceptable rates of side effects and with good short term biochemical disease control.

Chapter 8 Discussion

This chapter will now discuss the main outcomes of the study, further limitations and future trials.

8.1 Background

Radiotherapy for prostate cancer is effective but almost 50% of patients can develop biochemical failure within 7 years with the development of metastases with 5 years of this (3,89,131) . Further local therapy is an option for these men, however high morbidity rates such as urinary fistula (1%), rectal injury (9%) and bladder neck contracture (14%) associated with radical prostatectomy make it an unfavourable salvage treatment (132). There is an urgent need to deliver salvage treatment(s) with minimal side effects and optimum cancer control. Throughout this thesis the importance of accurate staging and localization of disease to deliver an appropriate salvage therapy has been discussed.

8.2 Limitations

8.2.1 Trial Limitations

There were several challenges that were faced during the setup and conduct of the FORECAST Study.

8.2.1.1 Patient selection

Radiotherapy treatment has transformed in the last two decades. Prior to the 1990s, EBRT was delivered in a 2D manner using X-ray and bony landmarks to guide treatment resulting in unknown dosages of radiotherapy delivered to other pelvic organs such as bladder and bowel. As a result, the development of 3D planning using CT allowed for more precise delivery decreasing genito-

urinary (GU) and gastrointestinal (GI) side effects. There has been a change in recommended radiation dosage. Prior to the 1990s it was limited to 64-70 Gy to minimise toxicity however studies have shown dose-escalation of 74-80 Gy to have improved disease-free survival (133). Kuban et al. (134) showed that in 5 year biochemical/clinical failure free survival was 73% vs. 50% at 10 years in patients receiving 78 Gy versus 70 Gy, ($p = 0.004$) respectively. Further advances in 3D conformational radiotherapy has led to intensity-modulated RT (IMRT) which delivers radiation beams in different angles at increased intensity whilst decreasing doses delivered to other organs at risk (133). Dose escalated IMRT of up to 80 Gy has reported 5-year biochemical relapse rate of 28% compared to 39% in those 70 Gy (135).

However higher radiation doses have resulted in higher ≥ grade 2 GI toxicity was 13% vs. 26% for patients treated with 70 Gy compared to those treated to 78 Gy ($p=0.013$) (133,134). Zelefesky et al. (136) compared IMRT and 3DCRT in ($n=171$ and $n= 61$ respectively) and reported 2-year actuarial risk of grade 2 bleeding was 2% for IMRT and 10% for conventional 3D-CRT ($P<0.001$). (Acute and late urinary (GI) and rectal (GU) toxicity was scored according to the Radiation Therapy Oncology Group morbidity grading scale) For patients who received 81 Gy in either treatment, IMRT still had lower acute GI toxicity compared to 3D-CRT (Grade 1 toxicity 33% vs. 46% and Grade 2 toxicity 12% vs. 15% $p=0.05$ respectively. Late rectal toxicity was better in the IMRT group 0.5% vs. 13% ($p=0.0001$) compared with 3DCRT group.

Brachytherapy has also been widely incorporated into treatment of prostate cancer. The direct delivery of radioactive sources into the prostate significantly reduces radiation doses to surrounding organs such as the bladder and rectum (133). Brachytherapy can be either high dose where there is temporary insertion of high energy radioactive isotope such as Iridium-192 or low dose where permanent seed implants (either Iodine-125 or Pallidium-103) are placed. Brachytherapy has the advantage of being used as a single therapy in low to intermediate risk cancer, but also as an adjuvant to EBRT in high risk cancer. Hoskin et al. (137) performed a randomised phase-III trial

compared external beam radiotherapy (EBRT) alone with EBRT combined with high-dose-rate brachytherapy boost (HDR-BTb). The biochemical relapse free survival rate at 7 years was higher in those who received the brachytherapy boost, compared to those who received EBRT alone 66% vs. 48% p=0.04 respectively.

Rodda et al. (138) examined side effects of dose escalation EBRT (up to 78 Gy) and ADT compared with low dose rate (LDR) brachytherapy boost. Late Effects of Normal Tissue Somatic, Objective, Management, Analytic (LENT-SOMA) scale was used to determine toxicity outcomes. The cumulative incidence of late grade 3 GU morbidity at 2 and 5 years was 7.7% and 18.4% for LDR brachytherapy boost, versus 3.4% and 5.2% for dose escalated EBRT $p < 0.01$. The prevalence of grade 3 GU morbidity after brachytherapy boost was 7.0% at 2 years and 8.6% at 5 years, compared with 1.1% at 2 years ($P = 0.005$) and 2.2% at 5 years ($p= 0.058$) for those who received dose escalated EBRT. Overall, it has been accepted that brachytherapy boost may be suitable in patients with more aggressive cancer for a higher likelihood of potential cure at the risk of bowel or urinary toxicity (133).

Hypofractionated radiotherapy which involves giving larger doses over a shorter period of time (119,133). Current standard of care for radiation doses include 75.6 Gy or higher, which is delivered in 1.8 to 2 Gy daily fractions delivering 75.6 Gy or higher, and so treatment duration us typically 8 to 9 weeks. Phase 3 of the RCT Conventional or hypofractionated high dose intensity modulated radiotherapy for prostate cancer (CHHIP) trial as reported by Dearnley et al. (139) delivered hypofractionation doses of or 57 Gy in 19 fractions over 3.8 weeks (n=1077), 60 Gy in 20 fractions over 4 weeks (n=1074) or 57 Gy in 19 fractions over 3.8 weeks (n=1077) in comparison with conventional 74 Gy delivered in 37 fractions over 7.4 weeks (n=1065). The 5-year biochemical or clinical failure-free rates were 85·9% (83.4 - 88.0) in the 57 Gy group, 90·6% (88.5 – 92.3) in the 60 Gy group and 88.3% (95% CI 86.0 – 90.2) in the 74 Gy group. According to (National Comprehensive Cancer Network (NCCN) low-risk, intermediate-risk, and high-risk groups had 5 year, biochemical and clinical failure-free rates were 90.9% (85.1 – 94.5), 86%

(83.1 – 88.5), and 78.3% (69.2 - 85) for the 57 Gy group, respectively 96.6% (92.1 – 98.6), 90.2% (87.7 – 92.3), and 84.2% (75.7 – 90.0) for the 60 Gy group; and 96.7% (95% CI 92.3 – 98.6), 86.8% (84.0 – 89.1), and 86.5% (78.4 – 91.7) for the 74 Gy group respectively (139). Hypofractionated radiotherapy was delivered with fewer treatments can increase the convenience for the patient and lower costs for the health care system. EAU (119) advises that only evidence based fractionation schedules should be used outside of clinical trials and higher doses such as 5-10 Gy per fraction delivered in five to seven fractions should still be considered as investigational.

Stereotactic body radiation therapy delivers 7 to 10 Gy per fraction and completing treatment in 4 to 5 total fractions. King et al. (140) performed a pooled analysis of multiple phase II trials which had total of 1,100 patients; these patients received a total of 35 to 40 Gy in 5 fractions or 39 Gy in 4 fractions. The 5-year biochemical relapse free survival rates (b-RFS) was 93% for patients receiving a dose 35 Gy vs. 90.7% for dose 36.25 Gy (p=0.08) and 95.8% for those doses 38 - 40 Gy (p=0.83). The 5-year b-RFS was 97% for this entire cohort, 99% for patients with low-risk and 93% for patients with intermediate-risk (p = 0.11).

Another form of radiotherapy is proton beam therapy. Protons have the ability of delivering high dose of radiation at a prescribed depth and then a rapid dose fall off after this point (133). There are few studies that provide survival data of proton therapy compared with standard radiation therapy. Therefore, at present it is unknown the likely recurrence rate and suitability of these patients for further salvage therapy.

Due to differences in patients' primary radiation treatment several issues arise when these patients are selected for further salvage treatment. Firstly, it is often difficult to gather primary D'Amico risk information, radiotherapy doses, accurate PSA levels following radiotherapy and the time of biochemical failure in patients who had treatment in the early 1990s. Differences in outcomes following FST therefore may be due to their baseline risk. The wide variation

between patients impedes analysis as it is difficult to group patients and therefore correlate those who may benefit from FST. Secondly, without this baseline data, patients may have had high doses of radiotherapy and thus may be at increased risk of significant side effects such as recto-urethral fistula. The introduction of brachytherapy and again the changes in types and radiation doses delivered have the same problems above.

8.2.1.2 Trial set-up and work flow

Gaining ethical approval for the number of initial scans was challenging. As patients are undergoing four initial diagnostic scans, this can be quite onerus on patients especially considering this requires two hospital visits. Standard of care options, would not typically require patients to undergo bone scan with PSA <20ng/ml. As discussed above this is unlikely to yield established metastatic disease and potentially exposing patients to radiation that was not yet warranted. This was overcome as several studies do indicate that salvage treatment should not be offered unless metastatic disease is ruled out and that is with Choline PET/CT+/- Bone scan and both are often performed in other experimental trials (37,56,70).

Whilst this did gain ethical approval, the same challenge of the number of initial scans was met by both imaging departments and patients. It was essential to co-ordinate patient scans in a timely and efficient manner, minimizing the number of visits but also dealing with the standard of care workload in both MRI and nuclear medicine departments. It was advised that patients could not have Choline PET/CT and bone scan on the same day, instead they had to be over two days. For patients travelling long distances this was sometimes difficult as they had to come back for two days incurring travel and accommodation expenses. This also delayed reporting and further management as patients could not sometimes attend two days in a row, but sometimes up to two weeks apart. However as above, normal investigations outside of the trial prior to any salvage treatment, would typically involve Choline PET/CT, bone scan and mpMRI would have been advised and therefore, a minimum of two visits were likely.

The reporting of scans for MDT pre-biopsy also posed some difficulty as time had to be set with the radiologists who had both clinical and research trial work. This could sometimes be delayed for up to two weeks which further delayed MDT discussion and importantly patient management. At time of MDT, extra time had to be allowed for FORECAST patients as – 3 scans had to be reviewed (WB-MRI to remain blinded) and patients discussed to determine suitability for salvage treatment, this again increased workload on all members of MDT. To help decrease burden on radiologists, images were electronically transferred to other hospitals where radiologists were working anonymised reports were sent back. To help decrease burden on MDT, only the research fellow responsible for FORECAST (myself) presented the cases as full clinical information was already known due to the initial patient visit. The clinical research fellow, could then co-ordinate further patient management based on MDT outcome – either book for biopsy or withdraw from the trial (for example if metastatic disease was present).

Another issue was the presence of metastatic disease which resulted in the exclusion of several patients post imaging. Although it was expected that 50% would be excluded, it did lead to poor recruitment and retainment numbers initially proceeding to further biopsy and treatment. This was overcome by setting up two further recruitment centres at Basingstoke and North Hampshire Hospital and Queen Elizabeth hospital in Kings Lynn. We were approached by these centres due to their interest in our trial and whilst Queen Elizabeth Hospitals could not offer focal salvage treatment, they could perform all other scans and biopsy and refer patients to us if still suitable for the salvage treatment. Basingstoke hospitals could offer salvage HIFU but those suitable for salvage cryotherapy, were referred to UCLH.

Another problem initially faced, was length of follow up. Obviously the greater the length of follow up, the more information available regarding biochemical recurrence and further disease progression. However, there is a risk of loss to follow up. To decrease burden on patients they had face to face follow up at 4 weeks and 12 months, the latter to coincide with final pelvic mpMRI. The

interim visits at 3, 6 and 9 months could be performed via telephone with local PSA results being forward on to our centre for data collection.

An important aspect of any treatment and particularly salvage treatment is evidence of recurrence. In this trial, we did not incorporate further biopsy at the end of one year follow up as it was not felt to be in the patients best interest.
Patients would be having a third general anaesthetic, perineal biopsies are known to be painful with some side effects of perineal bruising, haematuria and sepsis (141). Also, it is unlikely patients would undergo a third treatment to the prostate due to the increased risk of developing a rectourethral fistula. In relation to biopsy, we also could not justify bone biopsy in patients with metastatic disease. It is rare for this to be performed even as standard of care in metastatic prostate cancer, as it carries side effects such as pain, infection and bleeding. Although this would confirm the accuracy of the imaging tests, this was not incorporated in the trial. To overcome this, WB-MRI outcomes remains blinded till patients reach the end of the trial and was not used to dictate clinical decisions. Unlike previous trials discussed above in Section 3.2.6.3 where WB-MRI is used to dictate treatment alongside Choline PET/CT and bone scan (23). WB-MRI is yet to be validated and therefore novel imaging should not be used to alter patients' management until proven to be of high accuracy. Patients are offered to undergo a repeat WB-MRI as part of the LOCATE trial. At the end of both trials, comparison of WB-MRI to standard of care tests pre-and post-salvage treatment can show if metastatic disease was detected, and whether there was any regression or progression of metastatic disease following local treatment.

8.2.1.3 Advances in diagnostics

Other challenges have been the development of newer imaging tests and further molecular advances in the diagnosis of metastatic disease.
Advances in Choline PET/CT involves the development of a target radioligand that binds to Prostate Specific Membrane Antigen (PSMA). PSMA is a cell surface protein overexpressed in prostate cancer compared to other organs

such as the kidney, small intestine and salivary glands. (142). One study examined PSMA expression in 184 radical prostatectomy specimens without previous treatment and found an incremental increase in PSMA expression from benign epithelium to high-grade carcinoma (143,144).

Several studies have examined its use in recurrent cancer post primary treatment and have shown accuracies up to 89% (142,145). These studies however examine patients who have had differing primary treatments such as radical prostatectomy, radiotherapy and brachytherapy. One such study performed by Bluemel et al. (145) examined 125 patients who had PSA rise following primary treatment found that 68Ga-PSMA PET/CT identified a further 43.8% of patients with recurrent disease that 18F-choline-PET/CT had reported as negative. Thus, the combination of both scans had a detection rate of 85.6%. 18F-choline-PET/CT detected recurrence in 89.4% compared to 71.4% of patients by 68Ga-PSMA PET/CT with PSA >2ng/ml. A sequential approach of 18F-choline-PET/CT followed by 68Ga-PSMA PET/CT had the highest detection rate of detection with PSA >2ng/ml 97%. Another similar study performed by Verburg et al. found that 68Ga-PSMA PET/CT had a higher detection rate of recurrent lesions when PSA > 2ng/ml VS. <1ng/ml 89% vs. 44% ($p<0.001$). However, this study lacked histopathological confirmation and did not use verification scans.

Einspieler et al. examined the detection rate of 68Ga-PSMA PET/CT in 118 patients post radiotherapy. (146) 45 were patients were on ADT at time of scanning. The detection rates also increased with a higher PSA were 96.8% (30/31) for PSA ≥ 10ng/ml vs. 81.8% (36/44), for PSA of 2 to <5ng/ml ($p = 0.0377$). Surprisingly detection of recurrent cancers were higher in patients on ADT compared to those not on ADT 97.7% (44/45) of patients with ADT and 86.3% (63/73) ($p = 0.0381$), however the PSA was higher in the group receiving ADT compared to those not on ADT 7.7ng/ml (2.2-65.0, 4.6-15.6) (n=45) vs. 5.9 ng/ml (2.2-158.4, 3.9-8.9) (n=73). There is no discussion of the time from initiation of ADT to time of imaging. It is also unclear how many patients underwent histopathological confirmation but local (n=6) and metastatic recurrence (n=1) was confirmed. Further correlation studies were

performed (PET/CT, PET/MRI, BS, CT) in 29 patients. This was concordant with positive findings of 68Ga-PSMA PET/CT of metastatic or local recurrence. The study does not further expand on negative 68Ga-PSMA PET/CT and concordance with other local or distant imaging.

Currently there is a clear lack of guidance with PSMA-Choline PET/CT, there is potential in increasing diagnostic accuracy with sequential imaging alongside 18F-Choline. This was not initially available at the time of set up in FORECAST Study at our centre. As it is part of Choline PET/CT sequencing, it may be possible to perform this at the same time as 18F-Choline, Further discussion with nuclear medicine and ethical approval would have to be gained.

8.2.1.4 Circulating Tumour Cells

Circulating Tumour Cells (CTC) have been found to spread despite a carcinoma being in situ. (147). The problem with CTC is that they do not have the genomic abnormalities that characterize and do not evolve in parallel to the primary tumour. CTC are considered to be en-route to or from disseminated sites and reflective of metastasis and can be identified via blood sample (147). CTC undergo a transition from epithelial cells to mesenchymal cells (EMT – Epithelial to mesenchymal transition) in order to leave neighbouring epithelial cells and become more mobile, invasive, and capable of seeding (147). These are all hallmarks of increased malignancy. Once target organs (host tissues) are reached a reversal process need to occur from mesenchymal cells to an epithelial form, to regain their ability to proliferate (144,148). However, despite CTC circulating throughout the body, distant metastases only occur in a few sites, predominantly bone. Studies have reported on a complex paracrine/autocrine pathway allowing growth of metastatic prostate cancer cells within bone (144,149)**.** Studies suggest that 0.01% of circulating tumour cells can produce a single bone metastasis, and at least 104 circulating tumour cells are required for the development of a metastatic focus (144,150).

The identification of CTC has proved challenging. Reverse transcriptase polymerase chain reaction (RT-PCR) techniques have been used however presence of other cellular contaminants, such as red blood cells, normal epithelial cells, and leukocytes lower specificity (144). Immunomagnetic selection (IMS) techniques use nanometer-sized magnetic beads coated with cell-specific antibodies to target epithelial cell specific antigens. In prostate cancer, the epithelial cell-adhesion molecule (EpCAM) has been used (144) IMS detects only intact cells, whereas PCR detects living cells, dead cells, and free DNA, thus there is a risk of false-positive results. The CellSearch system, uses microscopic iron particles (called ferrofluids) coated with anti-EpCAM antibodies to immunomagnetically enrich epithelial cells in a peripheral blood sample drawn from a patient (144,151). The CellSearch System has been approved by the US Food and Drug Administration for use in breast, colorectal, and prostate cancer. CellSearch System has been examined in a few studies.

A study performed by Thalgott et al. (152) examined CTC in healthy controls, patients with metastatic, locally advanced and taxane refractory prostate cancer. The CellSearch technique was used to isolate CTC. Patients with bone and visceral disease had the highest CTC count 26 (range 0-207), however healthy controls and patients with soft tissue disease, had comparable CTC levels. Previously, a threshold of ≥ 5 CTCs per 7.5 ml venous blood was determined as prognostic significant for overall survival (OS) (152). Healthy controls had no CTC detected and only one patient in the locally advanced prostate cancer (LAPC) group had CTC detected. Patients with metastatic cancer had a median of 9 CTC and this was detected in 84% which was significantly elevated compared to controls and LAPC group ($p < 0.001$). Patients who had metastatic disease resistant to taxane therapy had a higher number of CTC present (n=15) (median number of 14 CTCs (range 0-2,437)) present in 93% of patients compared to those who had metastatic disease prior to starting docetaxel (n=14) (median CTC count of 7.5 (range 0-225)) in 80% of the group. Kaplan-Meier analyses demonstrated in metastatic patients with <5 CTCs a significantly longer OS compared to patients

harboring >5 CTCs (median 158 days; n = 32 (p = 0.003)). Focusing on the absolute PSA level, no correlation was found for CTC count.

8.2.1.5 Disseminated Tumour Cells

Bone marrow aspirate have been analysed to determine the presence of Disseminated Tumour Cells (DTC). Berg et al. (153) examined 266 patients who had bone marrow (BM) aspirate analysis at baseline prior to radiation treatment or hormonal treatment. DTCs were present in BM of 48 (18%) of the patients. Positive BM-status was significantly associated with increasing percentage of Gleason 4/5 cancer (p=0.04) and increasing Gleason Score (p = 0.04). 131 patients went on to have radiotherapy, and of these, BM was positive for DTCs in 20% (26/131) of patients. There were 12 deaths overall, 9 were prostate cancer related. 20 patients had failure following definitive EBRT, 6% (8/131) had locoregional failure and 9% (12/131) developed distant metastases. The 7-year cumulative risk of distant metastases as first clinical relapse was 21% for BM-positive patients vs. 6% for BM-negative patients (p = 0.07) (153). It is important to note that despite the number of DTC present, there was no higher risk of distant metastases with an increased number of DTC. Patients with Gleason Score ≥7 and positive BM had a higher 7-year cumulative risk of DM as first clinical relapse of 34% vs. 10% for those with negative BM (p = 0.04). 75 patients did not receive ADT following EBRT and 7-year cumulative risk of DM as first clinical relapse was 28% vs. 9% in those with positive BM versus negative BM respectively. However, in these patients, cancer related death had a 7-year cumulative risk of failure of 7% in those with positive BM vs. 9% risk in those with negative BM. There was no association with a higher PSA level or T-stage to the number of DTC or an increased rate of DM. This study also found that patients with a Gleason Score <7 did not develop distant metastases despite 10 patients having positive BM for DTC.

Whilst we would not perform bone marrow biopsy in our patients, as we want to minimise invasive procedures on our patients, we could perform peripheral blood sampling and use the Cell Search technique. This could easily be

incorporated at the initial clinical visit where patients have a sample taken for PSA. This would require further funding and ethical approval.

8.3 Strengths of the Study

Issues currently facing clinicians is guiding their patients to the best salvage treatment post radiotherapy. At present, there is no single best imaging test to diagnose radiorecurrent disease, no definition of clinically significant cancer post radiotherapy and several salvage treatment options available all with differing cancer control and side effect profiles.

A recent international consensus discussing the set up of prospective trials examining focal salvage ablative therapy (Salvage Ablative Trial SAT) (154) proposed the following objectives:

1) The primary objective of a SAT trial should be to assess the efficacy of the treatment for negative biopsy rate at 12 months posttreatment.

2) The secondary objectives include

    a. Assessment of quality of life (QOL);
    b. Treatment safety profile defined by adverse events and side effects;
    c. 3-year and long-term biochemical disease-free survival (b-DFS);
    d. Progression- free survival, defined as the time without findings of local recurrence or distant metastasis.

There was no agreed consensus on entry trial PSA nor minimum doubling time of PSA at inclusion. However, patients with a PSA nadir +2 plus positive prostate biopsy would be considered suitable for trial entry. Patients with all Gleason Grades should be included provided there was no extracapsular extension.

Salvage therapies to be examined included HIFU and cryotherapy in w hole gland, hemi-gland or focal ablative manner. Before inclusion, it was recommended to exclude metastases by performing bone scan MRI or Choline PET/CT. There was agreement that patients should be excluded if metastatic disease was present. Consensus was reached to stop androgen deprivation therapy and not to stop usage of 5α-reductase inhibitors.

Assessing QOL and baseline function using EPIC, the IIEF-5, and the IPSS was recommended.

mpMRI including diffusion-weighted imaging and dynamic contrast-enhanced imaging was recommended as the imaging technique to guide salvage ablative treatments.

Follow-up In the first-year post treatment, patients need to be followed up every 3 months with PSA check at these intervals. In the second year and the third year, patients should be followed up biannually and thereafter annually. The second year and thereafter, PSA testing has to be done twice a year with follow up mpMRI. Imaging and biopsies should be performed at time points based on the discretion of the investigators. Minimal duration for follow-up was recommended as 5 years.

The FORECAST study already incorporates several of these recommendations and follows patient through from biochemical failure post radiotherapy to potential further salvage treatment. This is the first prospective study that combines novel imaging, accurate characterization using template mapping biopsy and two focal salvage treatment options. The outcomes from this trial are likely to be substantial.

8.4 Future of FORECAST

8.4.1 Future Trials

FORECAST may allow for future randomized prospective trials. Patients who may not be eligible for treatment due to metastatic disease, could be randomized into trials examining surveillance vs. ADT vs. chemotherapy. These patients could all be followed up with further bone scan, Choline PET/CT and WB-MRI during this time to see the effectiveness of treatments providing further evidence to the accuracy of these techniques.

As discussed above, incorporation of new imaging techniques may be feasible, such as Choline PET/CT PMSA. This can be added alongside current Choline PET/CT sequences. Further expansion of the trial, if deemed accurate enough could be randomization of patients undergoing PSMA-Choline PET/CT and 18-F Choline – these could be further compared to see which is more accurate in the detection of metastatic disease.

Treatment of oligometastic disease in the primary setting is also being examined currently in the literature (155). However, there is no evidence of this in being effective/trialled in radiorecurrent disease. Using a combination of CTC and distant imaging tests, oligometastatic disease may be identified and targeted treatment or systemic treatment could occur to these metastases in combination with local treatment. Based on the outcomes of these treatments, patients who present with oligometastatic disease who are likely to benefit from further disease treatment and those who are likely to benefit from conservative management without the added risk of treatment burden can be managed accordingly.

Treatment of nodal disease is also being explored. Patients found to have nodal disease only could be treated with targeted focused treatment or hormonal therapy. Follow up with Choline PET/CT, Bone scan and WB-MRI

could determine the effectiveness of treatment and the accuracies of these imaging techniques.

Comparison of treatments of localized radiorecurrent disease could also be employed. Patients with high risk localized disease amenable to salvage radical prostatectomy, those with intermediate focal disease could be targeted with HIFU, Cryotherapy and brachytherapy. Follow up of these patients would determine cancer control of each salvage treatment and associated side effects. Analysing baseline and pre-salvage risk factors could allow for a prediction model to be formulated to determine the best treatment according to a patient's risk.

8.4.2 Risk Scoring and Prediction Modelling

At present, there is no definition of clinically significant cancer post radiotherapy. D'Amico risk score is commonly attributed but this is based on primary cancer setting and this system was developed on TRUS biopsy outcomes which is known to misclassify disease. This will be the first prospective study that can combine PSA, imaging and biopsy findings in radiorecurrent disease. These patients are likely to be followed up long term either because of salvage treatment or following the start of systemic therapy. Further analyses can then be performed to classify patients in a similar manner of low, intermediate and high risk following radiotherapy– a prediction model of those who are likely to benefit from local or systemic disease control can be calculated. This model using logistical regression, could incorporate baseline data and re-staging outcomes prior to salvage treatment to better stratify those patients who would benefit from systemic, nodal or local treatment.

8.5 Conclusion

In summary FORECAST is a prospective diagnostic and treatment trial which is likely to have significant implications on the management of patients with radiorecurrent prostate cancer.

Chapter 9 References

1. Guidelines on Prostate Cancer [[Internet]]. 09-Prostate-Cancer_LR.pdf. from: http://uroweb.org/wp-content/uploads/09-Prostate-Cancer_LR.pdf

2. Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, Stein KD, Alteri R, and Jemal A. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin. United States; 2016;66(4):271-89.

3. Zumsteg ZS, Spratt DE, Romesser PB, Pei X, Zhang Z, Polkinghorn W, McBride S, Kollmeier M, Yamada Y, and Zelefsky MJ. The Natural History and Predictors of Outcome Following Biochemical Relapse in the Dose Escalation Era for Prostate Cancer Patients Undergoing Definitive External Beam Radiotherapy. European Urology. Elsevier BV; 2015;67(6):1009-1016.

4. Ceci F, Castellucci P, Graziani T, Schiavina R, Brunocilla E, Mazzarotto R, Ntreta M, Lodi F, Martorana G, and Fanti S. 11C-choline PET/CT detects the site of relapse in the majority of prostate cancer patients showing biochemical recurrence after EBRT. Eur J Nucl Med Mol Imaging. Germany; 2014;41(5):878-86.

5. Khuntia D, Reddy CA, Mahadevan A, Klein EA, and Kupelian PA. Recurrence-free survival rates after external-beam radiotherapy for patients with clinical T1-T3 prostate carcinoma in the prostate-specific antigen era: what should we expect? Cancer. United States; 2004;100(6):1283-92.

6. Bolla M, Van Tienhoven G, Warde P, Dubois JB, Mirimanoff R, Storme G, Bernier J, Kuten A, Sternberg C, Billiet I, Torecilla JL, Pfeffer R, Cutajar CL, Van der Kwast T, and Collette L. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. The Lancet Oncology. Elsevier BV; 2010;11(11):1066-1073.

7. Chondrogiannis S, Marzola MC, Ferretti A, Maffione AM, Rampin L, Grassetto G, Nanni C, Colletti PM, and Rubello D. Role of ^{18}F-choline PET/CT in suspicion of relapse following definitive radiotherapy for prostate cancer. Eur J Nucl Med Mol Imaging. Germany; 2013;40(9):1356-64.

8. Kuban DA, Thames HD, Levy LB, Horwitz EM, Kupelian PA, Martinez AA, Michalski JM, Pisansky TM, Sandler HM, Shipley WU, Zelefsky MJ, and Zietman AL. Long-term multi-institutional analysis of stage T1–T2 prostate cancer treated with radiotherapy in the PSA era. International Journal of Radiation Oncology*Biology*Physics. Elsevier BV; 2003;57(4):915-928.

9. Roach M, Hanks G, Thames H, Schellhammer P, Shipley WU, Sokol GH, and Sandler H. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys. United States; 2006;65(4):965-74.

10. Cancer of the Prostate - SEER Stat Fact Sheets [[Internet]]. Cancer of the Prostate - SEER Stat Fact Sheets. [cited 2017]. Retrieved from: https://seer.cancer.gov/statfacts/html/prost.html

11. Jadvar H. Prostate cancer: PET with 18F-FDG, 18F- or 11C-acetate, and 18F- or 11C-choline. J Nucl Med. United States; 2011;52(1):81-9.

12. Duijzentkunst DA, Peters M, van der Voort van Zyp JR, Moerland MA, and van Vulpen M. Focal salvage therapy for local prostate cancer recurrences after primary radiotherapy: a comprehensive review. World J Urol. Germany; 2016;34(11):1521-1531.

13. Grossfeld GD, Li Y, Lubeck DP, Broering JM, Mehta SS, and Carroll PR. Predictors of Secondary Cancer Treatment in Patients Receiving Local Therapy for Prostate Cancer: Data From Cancer of the Prostate Strategic Urologic Research Endeavor. The Journal of Urology. Elsevier BV; 2002;168(2):530-535.

14. Agarwal PK, Sadetsky N, Konety BR, Resnick MI, and Carroll PR. Treatment failure after primary and salvage therapy for prostate cancer. Cancer. Wiley Subscription Services, Inc., A Wiley Company; 2008;112(2):307-314.

15. Saigal CS, Gore JL, Krupski TL, Hanley J, Schonlau M, Litwin MS, and Urologic Diseases in America Project. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. Cancer. United States; 2007;110(7):1493-500.

16. Thomas BC, and Neal DE. Androgen deprivation treatment in prostate cancer. BMJ. British Medical Journal Publishing Group; 2013;346:e8555.

17. Shahinian VB, Kuo YF, Freeman JL, and Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med. United States; 2005;352(2):154-64.

18. Choueiri TK, Dreicer R, Paciorek A, Carroll PR, and Konety B. A Model That Predicts the Probability of Positive Imaging in Prostate Cancer Cases With Biochemical Failure After Initial Definitive Local Therapy. The Journal of Urology. Elsevier BV; 2008;179(3):906-910.

19. Cher ML, Bianco FJ, lam JS, Davis LP, Grignon DJ, Sakr WA, Banerjee M, Pontes JE, and Wood DP. Limited role of radionuclide bone scintigraphy in patients with prostate specific antigen elevations after radical prostatectomy. The Journal of Urology. Elsevier BV; 1998;160(4):1387-1391.

20. Clamp A, Danson S, Nguyen H, Cole D, and Clemons M. Assessment of therapeutic response in patients with metastatic bone disease. The Lancet Oncology. Elsevier BV; 2004;5(10):607-616.

21. Taoka T, Mayr NA, Lee HJ, Yuh WT, Simonson TM, Rezai K, and Berbaum KS. Factors influencing visualization of vertebral metastases on MR

imaging versus bone scintigraphy. AJR. American journal of roentgenology. 2001;176(6):1525-1530.

22. Bubendorf L, Schöpfer A, Wagner U, Sauter G, Moch H, Willi N, Gasser TC, and Mihatsch MJ. Metastatic patterns of prostate cancer: An autopsy study of 1,589 patients. Human Pathology. Elsevier BV; 2000;31(5):578-583.

23. Lecouvet FE, El Mouedden J, Collette L, Coche E, Danse E, Jamar F, Machiels JP, Vande Berg B, Omoumi P, and Tombal B. Can whole-body magnetic resonance imaging with diffusion-weighted imaging replace Tc 99m bone scanning and computed tomography for single-step detection of metastases in patients with high-risk prostate cancer? Eur Urol. Switzerland; 2012;62(1):68-75.

24. Picchio M, Briganti A, Fanti S, Heidenreich A, Krause BJ, Messa C, Montorsi F, Reske SN, and Thalmann GN. The role of choline positron emission tomography/computed tomography in the management of patients with prostate-specific antigen progression after radical treatment of prostate cancer. Eur Urol. Switzerland; 2011;59(1):51-60.

25. Pflug BR, Pecher SM, Brink AW, Nelson JB, and Foster BA. Increased fatty acid synthase expression and activity during progression of prostate cancer in the TRAMP model. Prostate. United States; 2003;57(3):245-54.

26. Richter JA, Rodríguez M, Rioja J, Peñuelas I, Martí-Climent J, Garrastachu P, Quincoces G, Zudaire J, and García-Velloso MJ. Dual Tracer 11C-Choline and FDG-PET in the Diagnosis of Biochemical Prostate Cancer Relapse After Radical Treatment. Molecular Imaging and Biology. Springer-Verlag; 2009;12(2):210-217.

27. Müller SA, Holzapfel K, Seidl C, Treiber U, Krause BJ, and Senekowitsch-Schmidtke R. Characterization of choline uptake in prostate cancer cells following bicalutamide and docetaxel treatment. Eur J Nucl Med Mol Imaging. Germany; 2009;36(9):1434-42.

28. Watanabe H, Kanematsu M, Kondo H, Kako N, Yamamoto N, Yamada T, Goshima S, Hoshi H, and Bae KT. Preoperative detection of prostate cancer: A comparison with 11C- choline PET, 18F- fluorodeoxyglucose PET and MR imaging. Journal of Magnetic Resonance Imaging. Wiley Subscription Services, Inc., A Wiley Company; 2010;31(5):1151-1156.

29. Hodolic M, Cimitan M, and Fettich J. Importance of Gleason score on 18F-choline PET/CT findings in patients with biochemical relapse of prostate cancer disease (PSA< 1.0 ng/ml). Importance of Gleason score on 18F-choline PET/CT findings in patients with biochemical relapse of prostate cancer disease (PSA< 1.0 ng/ml). American Society of Clinical Oncology; 2013.

30. Koh D-M, TAKAHARA T, IMAI Y, and COLLINS DJ. Practical aspects of assessing tumors using clinical diffusion-weighted imaging in the body. Magnetic Resonance in Medical Sciences. Japanese Society for Magnetic Resonance in Medicine; 2007;6(4):211-224.

31. Komori T, Narabayashi I, Matsumura K, Matsuki M, Akagi H, Ogura Y, Aga F, and Adachi I. 2-[Fluorine-18]-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography versus whole-body diffusion-weighted MRI for detection of malignant lesions: initial experience. Ann Nucl Med. Japan; 2007;21(4):209-15.

32. Héliou R, Normandeau L, and Beaudoin G. Towards dose reduction in CT: patient radiation dose assessment for CT examinations at university health center in Canada and comparison with national diagnostic reference levels. Radiat Prot Dosimetry. England; 2012;148(2):202-10.

33. Crook J, Malone S, Perry G, Bahadur Y, Robertson S, and Abdolell M. Postradiotherapy prostate biopsies: what do they really mean? results for 498 patients. International Journal of Radiation Oncology*Biology*Physics. Elsevier BV; 2000;48(2):355-367.

34. Bostwick DG, Egbert BM, and Fajardo LF. Radiation injury of the normal and neoplastic prostate. Am J Surg Pathol. United States; 1982;6(6):541-51.

35. Miller EB, Ladaga LE, el-Mahdi AM, and Schellhammer PF. Reevaluation of prostate biopsy after definitive radiation therapy. Urology. United States; 1993;41(4):311-6.

36. Kimura M, Mouraviev V, Tsivian M, Mayes JM, Satoh T, and Polascik TJ. Current salvage methods for recurrent prostate cancer after failure of primary radiotherapy. BJU Int. England; 2010;105(2):191-201.

37. Boukaram C, and Hannoun-Levi JM. Management of prostate cancer recurrence after definitive radiation therapy. Cancer Treat Rev. Netherlands; 2010;36(2):91-100.

38. Scardino PT. The prognostic significance of biopsies after radiotherapy for prostatic cancer. Semin Urol. United States; 1983;1(4):243-52.

39. Onik G, and Barzell W. Transperineal 3D mapping biopsy of the prostate: an essential tool in selecting patients for focal prostate cancer therapy. Urol Oncol. United States; 2008;26(5):506-10.

40. Crawford ED, Wilson SS, Torkko KC, Hirano D, Stewart JS, Brammell C, Wilson RS, Kawata N, Sullivan H, Lucia MS, and Werahera PN. Clinical staging of prostate cancer: a computer-simulated study of transperineal prostate biopsy. BJU Int. England; 2005;96(7):999-1004.

41. Pinto PA, Chung PH, Rastinehad AR, Baccala AA, Kruecker J, Benjamin CJ, Xu S, Yan P, Kadoury S, Chua C, Locklin JK, Turkbey B, Shih JH, Gates SP, Buckner C, Bratslavsky G, Linehan WM, Glossop ND, Choyke PL, and Wood BJ. Magnetic resonance imaging/ultrasound fusion guided prostate biopsy improves cancer detection following transrectal ultrasound biopsy and correlates with multiparametric magnetic resonance imaging. J Urol. United States; 2011;186(4):1281-5.

42. Kasivisvanathan V, Dufour R, Moore CM, Ahmed HU, Abd-Alazeez M, Charman SC, Freeman A, Allen C, Kirkham A, van der Meulen J, and Emberton M. Transperineal magnetic resonance image targeted prostate biopsy versus transperineal template prostate biopsy in the detection of clinically significant prostate cancer. J Urol. United States; 2013;189(3):860-6.

43. Haider MA, Chung P, Sweet J, Toi A, Jhaveri K, Ménard C, Warde P, Trachtenberg J, Lockwood G, and Milosevic M. Dynamic contrast-enhanced magnetic resonance imaging for localization of recurrent prostate cancer after external beam radiotherapy. Int J Radiat Oncol Biol Phys. United States; 2008;70(2):425-30.

44. Arumainayagam N, Kumaar S, Ahmed HU, Moore CM, Payne H, Freeman A, Allen C, Kirkham A, and Emberton M. Accuracy of multiparametric magnetic resonance imaging in detecting recurrent prostate cancer after radiotherapy. BJU Int. England; 2010;106(7):991-7.

45. Kanthabalan A, Abd-Alazeez M, Arya M, Allen C, Freeman A, Jameson C, Kirkham A, Mitra AV, Payne H, Punwani S, Ramachandran N, Walkden M, Emberton M, and Ahmed HU. Transperineal Magnetic Resonance Imaging-targeted Biopsy versus Transperineal Template Prostate Mapping Biopsy in the Detection of Localised Radio-recurrent Prostate Cancer. Clin Oncol (R Coll Radiol). England; 2016;28(9):568-76.

46. Bianco FJ, Scardino PT, Stephenson AJ, Diblasio CJ, Fearn PA, and Eastham JA. Long-term oncologic results of salvage radical prostatectomy for locally recurrent prostate cancer after radiotherapy. Int J Radiat Oncol Biol Phys. United States; 2005;62(2):448-53.

47. Touma NJ, Izawa JI, and Chin JL. Current status of local salvage therapies following radiation failure for prostate cancer. J Urol. United States; 2005;173(2):373-9.

48. Grado GL, Collins JM, Kriegshauser JS, Balch CS, Grado MM, Swanson GP, Larson TR, Wilkes MM, and Navickis RJ. Salvage brachytherapy for localized prostate cancer after radiotherapy failure. Urology. United States; 1999;53(1):2-10.

49. Aaronson DS, Yamasaki I, Gottschalk A, Speight J, Roach M, and Shinohara K. Salvage Permanent Perineal Radioactive Seed Implantation for the Treatment of Localized Prostate Adenocarcinoma Recurrence after External Beam Radiation. International Journal of Radiation Oncology*Biology*Physics. Elsevier BV; 2008;72(1):S310.

50. Ismail M, Ahmed S, Kastner C, and Davies J. Salvage cryotherapy for recurrent prostate cancer after radiation failure: a prospective case series of the first 100 patients. BJU Int. England; 2007;100(4):760-4.

51. Pisters LL, Rewcastle JC, Donnelly BJ, Lugnani FM, Katz AE, and Jones JS. Salvage prostate cryoablation: initial results from the cryo on-line data registry. J Urol. United States; 2008;180(2):559-63; discussion 563-4.

52. Ahmed S, Lindsey B, and Davies J. Salvage cryosurgery for locally recurrent prostate cancer following radiotherapy. Prostate Cancer Prostatic Dis. England; 2005;8(1):31-5.

53. Galosi AB, Lugnani F, and Muzzonigro G. Salvage cryosurgery for recurrent prostate carcinoma after radiotherapy. Journal of endourology. 2007;21(1):1-7.

54. Ng CK, Moussa M, Downey DB, and Chin JL. Salvage cryoablation of the prostate: followup and analysis of predictive factors for outcome. J Urol. United States; 2007;178(4 Pt 1):1253-7; discussion 1257.

55. Nguyen PL, D'Amico AV, Lee AK, and Suh WW. Patient selection, cancer control, and complications after salvage local therapy for postradiation

prostate-specific antigen failure: a systematic review of the literature. Cancer. United States; 2007;110(7):1417-28.

56. Murat FJ, Poissonnier L, Rabilloud M, Belot A, Bouvier R, Rouviere O, Chapelon JY, and Gelet A. Mid-term results demonstrate salvage high-intensity focused ultrasound (HIFU) as an effective and acceptably morbid salvage treatment option for locally radiorecurrent prostate cancer. Eur Urol. Switzerland; 2009;55(3):640-7.

57. Uddin Ahmed H, Cathcart P, Chalasani V, Williams A, McCartan N, Freeman A, Kirkham A, Allen C, Chin J, and Emberton M. Whole-gland salvage high-intensity focused ultrasound therapy for localized prostate cancer recurrence after external beam radiation therapy. Cancer. United States; 2012;118(12):3071-8.

58. Chalasani V, Martinez CH, Lim D, and Chin J. Salvage HIFU for recurrent prostate cancer after radiotherapy. Prostate Cancer Prostatic Dis. England; 2009;12(2):124-9.

59. Rebillard X, Soulié M, Chartier-Kastler E, Davin JL, Mignard JP, Moreau JL, Coulange C, and Association Francaise d'Urologie. High-intensity focused ultrasound in prostate cancer; a systematic literature review of the French Association of Urology. BJU Int. England; 2008;101(10):1205-13.

60. Gelet A, Chapelon JY, Poissonnier L, Bouvier R, Rouvière O, Curiel L, Janier M, and Vallancien G. Local recurrence of prostate cancer after external beam radiotherapy: early experience of salvage therapy using high-intensity focused ultrasonography. Urology. United States; 2004;63(4):625-9.

61. Huang WC, Kuroiwa K, Serio AM, Bianco FJ, Fine SW, Shayegan B, Scardino PT, and Eastham JA. The anatomical and pathological characteristics of irradiated prostate cancers may influence the oncological efficacy of salvage ablative therapies. J Urol. United States; 2007;177(4):1324-9; quiz 1591.

62. Ahmed HU, Akin O, Coleman JA, Crane S, Emberton M, Goldenberg L, Hricak H, Kattan MW, Kurhanewicz J, Moore CM, Parker C, Polascik TJ, Scardino P, van As N, Villers A, and Transatlantic Consensus Group on Active Surveillance and Focal Therapy for Prostate Cancer (appendix). Transatlantic Consensus Group on active surveillance and focal therapy for prostate cancer. BJU Int. England; 2012;109(11):1636-47.

63. Leibovici D, Chiong E, Pisters LL, Guo CC, Ward JF, Andino L, Prokhorova IN, and Troncoso P. Pathological characteristics of prostate cancer recurrence after radiation therapy: implications for focal salvage therapy. J Urol. United States; 2012;188(1):98-102.

64. Darko Pucar Prostate cancer: Correlation of MR imaging and MR spectroscopy with pathologic findings after radiation therapy—initial experience. Radiology 2005, Aug;236(2):545. This will be incorporated.

65. Cellini N, Morganti AG, Mattiucci GC, Valentini V, Leone M, Luzi S, Manfredi R, Dinapoli N, Digesu' C, and Smaniotto D. Analysis of intraprostatic failures in patients treated with hormonal therapy and radiotherapy: implications for conformal therapy planning. Int J Radiat Oncol Biol Phys. United States; 2002;53(3):595-9.

66. Ahmed HU. The Index Lesion and the Origin of Prostate Cancer. N Engl J Med [[Internet]]. Massachusetts Medical Society; 2009;361(17):1704-1706. from: http://dx.doi.org/10.1056/NEJMcibr0905562

67. Ahmed HU, Arya M, Freeman A, and Emberton M. Do low-grade and low-volume prostate cancers bear the hallmarks of malignancy? Lancet Oncol. England; 2012;13(11):e509-17.

68. Peters M, Maenhout M, van der Voort van Zyp JR, Moerland MA, Moman MR, Steuten LM, van Deursen MJ, and van Vulpen M. Focal salvage iodine 125 brachytherapy for prostate cancer recurrences after primary radiotherapy:

A retrospective study regarding toxicity, biochemical outcome and quality of life. Radiotherapy and Oncology. Elsevier BV; 2014;112(1):77-82.

69. Eisenberg ML, and Shinohara K. Partial Salvage Cryoablation of the Prostate for Recurrent Prostate Cancer After Radiotherapy Failure. Urology. Elsevier BV; 2008;72(6):1315-1318.

70. Ahmed HU, Cathcart P, McCartan N, Kirkham A, Allen C, Freeman A, and Emberton M. Focal salvage therapy for localized prostate cancer recurrence after external beam radiotherapy: a pilot study. Cancer. United States; 2012;118(17):4148-55.

71. Wilson LS, Tesoro R, Elkin EP, Sadetsky N, Broering JM, Latini DM, DuChane J, Mody RR, and Carroll PR. Cumulative cost pattern comparison of prostate cancer treatments. Cancer. United States; 2007;109(3):518-27.

72. Boyd KA, Jones RJ, Paul J, Birrell F, Briggs AH, and Leung HY. Decision analytic cost-effectiveness model to compare prostate cryotherapy to androgen deprivation therapy for treatment of radiation recurrent prostate cancer. BMJ Open. England; 2015;5(10):e007925.

73. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, and Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. Bmj. British Medical Journal Publishing Group; 2008;337:a1655.

74. Barzell WE, and Melamed MR. Appropriate Patient Selection in the Focal Treatment of Prostate Cancer: The Role of Transperineal 3-Dimensional Pathologic Mapping of the Prostate—A 4-Year Experience. Urology. Elsevier BV; 2007;70(6):S27-S35.

75. Mottet N, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, Schmid HP, van der Kwast T, Wiegel T, Zattoni F, and Heidenreich A. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-

resistant prostate cancer. Actas Urológicas Españolas (English Edition). Elsevier BV; 2011;35(10):565-579.

76. Fricke E, Machtens S, Hofmann M, van den Hoff J, Bergh S, Brunkhorst T, Meyer GJ, Karstens JH, Knapp WH, and Boerner AR. Positron emission tomography with 11C-acetate and 18F-FDG in prostate cancer patients. Eur J Nucl Med Mol Imaging. Germany; 2003;30(4):607-11.

77. McHugh ML. Interrater reliability: the kappa statistic. Biochem Med (Zagreb). Croatia; 2012;22(3):276-82.

78. Picchio M, Spinapolice EG, Fallanca F, Crivellaro C, Giovacchini G, Gianolli L, and Messa C. [11C]Choline PET/CT detection of bone metastases in patients with PSA progression after primary treatment for prostate cancer: comparison with bone scintigraphy. Eur J Nucl Med Mol Imaging. Germany; 2012;39(1):13-26.

79. Poulsen MH, Petersen H, Høilund-Carlsen PF, Jakobsen JS, Gerke O, Karstoft J, Steffansen SI, and Walter S. Spine metastases in prostate cancer: comparison of technetium-99m-MDP whole-body bone scintigraphy,[18F] choline positron emission tomography (PET)/computed tomography (CT) and [18F] NaF PET/CT. BJU international. Wiley Online Library; 2014;114(6):818-823.

80. Evangelista L, Cimitan M, Hodolič M, Baseric T, Fettich J, and Borsatti E. The ability of 18F-choline PET/CT to identify local recurrence of prostate cancer. Abdominal Imaging. Springer US; 2015;40(8):3230-3237.

81. Umbehr MH, Müntener M, Hany T, Sulser T, and Bachmann LM. The Role of 11C-Choline and 18F-Fluorocholine Positron Emission Tomography (PET) and PET/CT in Prostate Cancer: A Systematic Review and Meta-analysis. European Urology. Elsevier BV; 2013;64(1):106-117.

82. Suva LJ, Washam C, Nicholas RW, and Griffin RJ. Bone metastasis: mechanisms and therapeutic opportunities. Nat Rev Endocrinol. England; 2011;7(4):208-18.

83. Venkitaraman R, Cook GJ, Dearnaley DP, Parker CC, Khoo V, Eeles R, Huddart RA, Horwich A, and Sohaib SA. Whole-body magnetic resonance imaging in the detection of skeletal metastases in patients with prostate cancer. J Med Imaging Radiat Oncol. Australia; 2009;53(3):241-7.

84. An H, Tao N, Li J, Guan Y, Wang W, Wang Y, and Wang F. Detection of Prostate Cancer Metastasis by Whole Body Magnetic Resonance Imaging Combined with Bone Scintigraphy and PSA Levels. Cellular Physiology and Biochemistry. Karger Publishers; 2016;40(5):1052-1062.

85. Barchetti F, Stagnitti A, Megna V, Al Ansari N, Marini A, Musio D, Monti ML, Barchetti G, Tombolini V, Catalano C, and Panebianco V. Unenhanced whole-body MRI versus PET-CT for the detection of prostate cancer metastases after primary treatment. Eur Rev Med Pharmacol Sci. Italy; 2016;20(18):3770-3776.

86. Conde-Moreno AJ, Herrando-Parreño G, Muelas-Soria R, Ferrer-Rebolleda J, Broseta-Torres R, Cozar-Santiago MP, García-Piñón F, and Ferrer-Albiach C. Whole-body diffusion-weighted magnetic resonance imaging (WB-DW-MRI) vs choline-positron emission tomography-computed tomography (choline-PET/CT) for selecting treatments in recurrent prostate cancer. Clin Transl Oncol. Italy; 2016;.

87. Spratt DE, Pei X, Yamada J, Kollmeier MA, Cox B, and Zelefsky MJ. Long-term survival and toxicity in patients treated with high-dose intensity modulated radiation therapy for localized prostate cancer. Int J Radiat Oncol Biol Phys. United States; 2013;85(3):686-92.

88. Merrick GS, Gutman S, Andreini H, Taubenslag W, Lindert DL, Curtis R, Adamovich E, Anderson R, Allen Z, Butler W, and Wallner K. Prostate cancer distribution in patients diagnosed by transperineal template-guided saturation biopsy. Eur Urol. Switzerland; 2007;52(3):715-23.

89. Morgan PB, Hanlon AL, Horwitz EM, Buyyounouski MK, Uzzo RG, and Pollack A. Timing of biochemical failure and distant metastatic disease for low-, intermediate-, and high-risk prostate cancer after radiotherapy. Cancer. United States; 2007;110(1):68-80.

90. Tanimoto A, Nakashima J, Kohno H, Shinmoto H, and Kuribayashi S. Prostate cancer screening: the clinical value of diffusion-weighted imaging and dynamic MR imaging in combination with T2-weighted imaging. J Magn Reson Imaging. United States; 2007;25(1):146-52.

91. van Dorsten FA, van der Graaf M, Engelbrecht MR, van Leenders GJ, Verhofstad A, Rijpkema M, de la Rosette JJ, Barentsz JO, and Heerschap A. Combined quantitative dynamic contrast-enhanced MR imaging and (1)H MR spectroscopic imaging of human prostate cancer. J Magn Reson Imaging. United States; 2004;20(2):279-87.

92. Abd-Alazeez M, Ramachandran N, Dikaios N, Ahmed HU, Emberton M, Kirkham A, Arya M, Taylor S, Halligan S, and Punwani S. Multiparametric MRI for detection of radiorecurrent prostate cancer: added value of apparent diffusion coefficient maps and dynamic contrast-enhanced images. Prostate Cancer Prostatic Dis. England; 2015;18(2):128-36.

93. Donati OF, Jung SI, Vargas HA, Gultekin DH, Zheng J, Moskowitz CS, Hricak H, Zelefsky MJ, and Akin O. Multiparametric prostate MR imaging with T2-weighted, diffusion-weighted, and dynamic contrast-enhanced sequences: are all pulse sequences necessary to detect locally recurrent prostate cancer after radiation therapy? Radiology. United States; 2013;268(2):440-50.

94. Kara T, Akata D, Akyol F, Karçaaltıncaba M, and Özmen M. The value of dynamic contrast-enhanced MRI in the detection of recurrent prostate cancer after external beam radiotherapy: correlation with transrectal ultrasound and pathological findings. Diagn Interv Radiol. Turkey; 2011;17(1):38-43.

95. Moore CM, Kasivisvanathan V, Eggener S, Emberton M, Fütterer JJ, Gill IS, Grubb III RL, Hadaschik B, Klotz L, Margolis DJ, Marks LS, Melamed J, Oto A, Palmer SL, Pinto P, Puech P, Punwani S, Rosenkrantz AB, Schoots IG, Simon R, Taneja SS, Turkbey B, Ukimura O, van der Meulen J, Villers A, and Watanabe Y. Standards of Reporting for MRI-targeted Biopsy Studies (START) of the Prostate: Recommendations from an International Working Group. European Urology. Elsevier BV; 2013;64(4):544-552.

96. Dickinson L, Ahmed HU, Allen C, Barentsz JO, Carey B, Futterer JJ, Heijmink SW, Hoskin PJ, Kirkham A, Padhani AR, Persad R, Puech P, Punwani S, Sohaib AS, Tombal B, Villers A, van der Meulen J, and Emberton M. Magnetic resonance imaging for the detection, localisation, and characterisation of prostate cancer: recommendations from a European consensus meeting. Eur Urol. Switzerland; 2011;59(4):477-94.

97. Barentsz JO, Richenberg J, Clements R, Choyke P, Verma S, Villeirs G, Rouviere O, Logager V, Fütterer JJ, and European Society of Urogenital Radiology. ESUR prostate MR guidelines 2012. Eur Radiol. Germany; 2012;22(4):746-57.

98. Kirkham AP, Haslam P, Keanie JY, McCafferty I, Padhani AR, Punwani S, Richenberg J, Rottenberg G, Sohaib A, Thompson P, Turnbull LW, Kurban L, Sahdev A, Clements R, Carey BM, and Allen C. Prostate MRI: who, when, and how? Report from a UK consensus meeting. Clin Radiol. England; 2013;68(10):1016-23.

99. Ahmed HU, Hu Y, Carter T, Arumainayagam N, Lecornet E, Freeman A, Hawkes D, Barratt DC, and Emberton M. Characterizing clinically significant prostate cancer using template prostate mapping biopsy. J Urol. United States; 2011;186(2):458-64.

100. Crook JM, Perry GA, Robertson S, and Esche BA. Routine prostate biopsies following radiotherapy for prostate cancer: results for 226 patients. Urology. United States; 1995;45(4):624-31; discussion 631-2.

101. Morgan VA, Riches SF, Giles S, Dearnaley D, and deSouza NM. Diffusion-weighted MRI for locally recurrent prostate cancer after external beam radiotherapy. AJR Am J Roentgenol. United States; 2012;198(3):596-602.

102. Rud E, Baco E, Lien D, Klotz D, and Eggesbø HB. Detection of radiorecurrent prostate cancer using diffusion-weighted imaging and targeted biopsies. AJR Am J Roentgenol. United States; 2014;202(3):W241-6.

103. Radtke JP, Kuru TH, Boxler S, Alt CD, Popeneciu IV, Huettenbrink C, Klein T, Steinemann S, Bergstraesser C, Roethke M, Roth W, Schlemmer H, Hohenfellner M, and Hadaschik BA. Comparative Analysis of Transperineal Template Saturation Prostate Biopsy Versus Magnetic Resonance Imaging Targeted Biopsy with Magnetic Resonance Imaging-Ultrasound Fusion Guidance. The Journal of Urology. Elsevier BV; 2015;193(1):87-94.

104. Siddiqui MM, Rais-Bahrami S, Truong H, Stamatakis L, Vourganti S, Nix J, Hoang AN, Walton-Diaz A, Shuch B, Weintraub M, Kruecker J, Amalou H, Turkbey B, Merino MJ, Choyke PL, Wood BJ, and Pinto PA. Magnetic resonance imaging/ultrasound-fusion biopsy significantly upgrades prostate cancer versus systematic 12-core transrectal ultrasound biopsy. Eur Urol. Switzerland; 2013;64(5):713-9.

105. Moore CM, Robertson NL, Arsanious N, Middleton T, Villers A, Klotz L, Taneja SS, and Emberton M. Image-guided prostate biopsy using magnetic resonance imaging-derived targets: a systematic review. Eur Urol. Switzerland; 2013;63(1):125-40.

106. Valerio M, Donaldson I, Emberton M, Ehdaie B, Hadaschik BA, Marks LS, Mozer P, Rastinehad AR, and Ahmed HU. Detection of Clinically Significant Prostate Cancer Using Magnetic Resonance Imaging-Ultrasound Fusion Targeted Biopsy: A Systematic Review. Eur Urol. Switzerland; 2015;68(1):8-19.

107. Kanthabalan A, Arya M, Punwani S, Freeman A, Haroon A, Bomanji J, Emberton M, and Ahmed HU. Role of focal salvage ablative therapy in localised radiorecurrent prostate cancer. World J Urol. Germany; 2013;31(6):1361-8.

108. Rouvière O, Valette O, Grivolat S, Colin-Pangaud C, Bouvier R, Chapelon JY, Gelet A, and Lyonnet D. Recurrent prostate cancer after external beam radiotherapy: value of contrast-enhanced dynamic MRI in localizing intraprostatic tumor—correlation with biopsy findings. Urology. Elsevier BV; 2004;63(5):922-927.

109. Wu LM, Xu J-, Gu HY, Hua J, Zhu J, Chen J, Zhang W, and Hu J. Role of Magnetic Resonance Imaging in the Detection of Local Prostate Cancer Recurrence after External Beam Radiotherapy and Radical Prostatectomy. Clinical Oncology. Elsevier BV; 2013;25(4):252-264.

110. Yakar D, Hambrock T, Huisman H, Hulsbergen-van de Kaa CA, van Lin E, Vergunst H, Hoeks CM, van Oort IM, Witjes JA, Barentsz JO, and Fütterer JJ. Feasibility of 3T dynamic contrast-enhanced magnetic resonance-guided biopsy in localizing local recurrence of prostate cancer after external beam radiation therapy. Invest Radiol. United States; 2010;45(3):121-5.

111. Ménard C, Iupati D, Publicover J, Lee J, Abed J, O'Leary G, Simeonov A, Foltz WD, Milosevic M, Catton C, Morton G, Bristow R, Bayley A, Atenafu EG, Evans AJ, Jaffray DA, Chung P, Brock KK, and Haider MA. MR-guided prostate biopsy for planning of focal salvage after radiation therapy. Radiology. United States; 2015;274(1):181-91.

112. Parekh A, Graham PL, and Nguyen PL. Cancer Control and Complications of Salvage Local Therapy After Failure of Radiotherapy for Prostate Cancer: A Systematic Review. Seminars in Radiation Oncology. Elsevier BV; 2013;23(3):222-234.

113. Kanthabalan A, Shah T, Arya M, Punwani S, Bomanji J, Haroon A, Illing RO, Latifoltojar A, Freeman A, Jameson C, van der Meulen J, Charman S, Emberton M, and Ahmed HU. The FORECAST Study - Focal Recurrent Assessment and Salvage Treatment for Radiorecurrent Prostate Cancer. Contemp Clin Trials. 2015;.

114. Ahmed HU, Berge V, Bottomley D, Cross W, Heer R, Kaplan R, Leslie T, Parker C, Relton C, Stephens R, Sydes MR, Turnbull L, van der Meulen J, Vickers A, Wilt T, Emberton M, and Prostate Cancer RCT Consensus Group. Can we deliver randomized trials of focal therapy in prostate cancer? Nat Rev Clin Oncol. England; 2014;11(8):482-91.

115. Chade DC, Eastham J, Graefen M, Hu JC, Karnes RJ, Klotz L, Montorsi F, van Poppel H, Scardino PT, and Shariat SF. Cancer control and functional outcomes of salvage radical prostatectomy for radiation-recurrent prostate cancer: a systematic review of the literature. Eur Urol. Switzerland; 2012;61(5):961-71.

116. Tran H, Kwok J, Pickles T, Tyldesley S, and Black PC. Underutilization of local salvage therapy after radiation therapy for prostate cancer. Urol Oncol. United States; 2014;32(5):701-6.

117. Nguyen PL, Alibhai SM, Basaria S, D'Amico AV, Kantoff PW, Keating NL, Penson DF, Rosario DJ, Tombal B, and Smith MR. Adverse effects of androgen deprivation therapy and strategies to mitigate them. Eur Urol. Switzerland; 2015;67(5):825-36.

118. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, Mason M, Matveev V, Wiegel T, Zattoni F, Mottet N, and European Association of Urology. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol. Switzerland; 2014;65(2):467-79.

119. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, Fossati N, Gross T, Henry AM, Joniau S, Lam TB, Mason MD, Matveev VB, Moldovan PC, van den Bergh RC, Van den Broeck T, van der Poel HG, van der Kwast TH, Rouvière O, Schoots IG, Wiegel T, and Cornford P. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol. Switzerland; 2016;.

120. Litwin MS, Hays RD, Fink A, Ganz PA, Leake B, and Brook RH. The UCLA Prostate Cancer Index: development, reliability, and validity of a health-related quality of life measure. Med Care. United States; 1998;36(7):1002-12.

121. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, and Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology. United States; 1997;49(6):822-30.

122. R: The R Project for Statistical Computing [[Internet]]. R: The R Project for Statistical Computing. [cited 2017]. Retrieved from: https://www.r-project.org/

123. Valerio M, Anele C, Charman SC, van der Meulen J, Freeman A, Jameson C, Singh PB, Emberton M, and Ahmed HU. Transperineal template prostate-mapping biopsies: an evaluation of different protocols in the detection of clinically significant prostate cancer. BJU Int. England; 2016;118(3):384-90.

124. Bott SR, Ahmed HU, Hindley RG, Abdul-Rahman A, Freeman A, and Emberton M. The index lesion and focal therapy: an analysis of the pathological characteristics of prostate cancer. BJU Int. England; 2010;106(11):1607-11.

125. Hu Y, Ahmed HU, Carter T, Arumainayagam N, Lecornet E, Barzell W, Freeman A, Nevoux P, Hawkes DJ, Villers A, Emberton M, and Barratt DC. A biopsy simulation study to assess the accuracy of several transrectal ultrasonography (TRUS)-biopsy strategies compared with template prostate

mapping biopsies in patients who have undergone radical prostatectomy. BJU Int. England; 2012;110(6):812-20.

126. Roy C, Foudi F, Charton J, Jung M, Lang H, Saussine C, and Jacqmin D. Comparative sensitivities of functional MRI sequences in detection of local recurrence of prostate carcinoma after radical prostatectomy or external-beam radiotherapy. AJR Am J Roentgenol. United States; 2013;200(4):W361-8.

127. Dickinson L, Ahmed HU, Hindley RG, McCartan N, Freeman A, Allen C, Emberton M, and Kirkham AP. Prostate-specific antigen vs. magnetic resonance imaging parameters for assessing oncological outcomes after high intensity-focused ultrasound focal therapy for localized prostate cancer. Urol Oncol. United States; 2017;35(1):30.e9-30.e15.

128. Shah TT, Ahmed H, Kanthabalan A, Lau B, Ghei M, Maraj B, and Arya M. Focal cryotherapy of localized prostate cancer: a systematic review of the literature. Expert Rev Anticancer Ther. England; 2014;14(11):1337-47.

129. Wei JT, Dunn RL, Litwin MS, Sandler HM, and Sanda MG. Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. Urology. United States; 2000;56(6):899-905.

130. Kanthabalan A, Peters M, Van Vulpen M, McCartan N, Hindley RG, Emara A, Moore CM, Arya M, Emberton M, and Ahmed HU. Focal salvage high-intensity focused ultrasound in radiorecurrent prostate cancer. BJU Int. England; 2017;.

131. Zelefsky MJ, Yamada Y, Fuks Z, Zhang Z, Hunt M, Cahlon O, Park J, and Shippy A. Long-term results of conformal radiotherapy for prostate cancer: impact of dose escalation on biochemical tumor control and distant metastases-free survival outcomes. Int J Radiat Oncol Biol Phys. United States; 2008;71(4):1028-33.

132. Gotto GT, Yunis LH, Vora K, Eastham JA, Scardino PT, and Rabbani F. Impact of prior prostate radiation on complications after radical prostatectomy. J Urol. United States; 2010;184(1):136-42.

133. Moon DH, Efstathiou JA, and Chen RC. What is the best way to radiate the prostate in 2016? Urol Oncol. United States; 2017;35(2):59-68.

134. Kuban DA, Tucker SL, Dong L, Starkschall G, Huang EH, Cheung MR, Lee AK, and Pollack A. Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. Int J Radiat Oncol Biol Phys. United States; 2008;70(1):67-74.

135. Beckendorf V, Guerif S, Prisé EL, Cosset J-M, Bougnoux A, Chauvet B, Salem N, Chapet O, Bourdain S, Bachaud J-M, Maingon P, Hannoun-Levi J-M, Malissard L, Simon J-M, Pommier P, Hay M, Dubray B, Lagrange J-L, Luporsi E, and Bey P. 70 Gy Versus 80 Gy in Localized Prostate Cancer: 5-Year Results of GETUG 06 Randomized Trial. International Journal of Radiation Oncology • Biology • Physics. Elsevier; 2011;80(4):1056-1063.

136. Zelefsky MJ, Fuks Z, Happersett L, Lee HJ, Ling CC, Burman CM, Hunt M, Wolfe T, Venkatraman ES, Jackson A, Skwarchuk M, and Leibel SA. Clinical experience with intensity modulated radiation therapy (IMRT) in prostate cancer. Radiotherapy and Oncology. Elsevier; 2000;55(3):241-249.

137. Hoskin PJ, Rojas AM, Bownes PJ, Lowe GJ, Ostler PJ, and Bryant L. Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. Radiother Oncol. Ireland; 2012;103(2):217-22.

138. Rodda S, Tyldesley S, Morris WJ, Keyes M, Halperin R, Pai H, McKenzie M, Duncan G, Morton G, Hamm J, and Murray N. ASCENDE-RT: An Analysis of Treatment-Related Morbidity for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost with a Dose-Escalated External Beam Boost

for High- and Intermediate-Risk Prostate Cancer. International Journal of Radiation Oncology • Biology • Physics. Elsevier; 2017;98(2):286-295.

139. Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, Graham J, Kirkbride P, Logue J, Malik Z, Money-Kyrle J, O'Sullivan JM, Panades M, Parker C, Patterson H, Scrase C, Staffurth J, Stockdale A, Tremlett J, Bidmead M, Mayles H, Naismith O, South C, Gao A, Cruickshank C, Hassan S, Pugh J, Griffin C, Hall E, and CHHiP Investigators. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol. England; 2016;17(8):1047-1060.

140. King CR, Freeman D, Kaplan I, Fuller D, Bolzicco G, Collins S, Meier R, Wang J, Kupelian P, Steinberg M, and Katz A. Stereotactic body radiotherapy for localized prostate cancer: pooled analysis from a multi-institutional consortium of prospective phase II trials. Radiother Oncol. Ireland; 2013;109(2):217-21.

141. Kanthabalan A, Emberton M, and Ahmed HU. Biopsy strategies for selecting patients for focal therapy for prostate cancer. Curr Opin Urol. United States; 2014;24(3):209-17.

142. Afshar-Oromieh A, Avtzi E, Giesel FL, Holland-Letz T, Linhart HG, Eder M, Eisenhut M, Boxler S, Hadaschik BA, Kratochwil C, Weichert W, Kopka K, Debus J, and Haberkorn U. The diagnostic value of PET/CT imaging with the (68)Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging. Germany; 2015;42(2):197-209.

143. Bostwick DG, Pacelli A, Blute M, Roche P, and Murphy GP. Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. Cancer. United States; 1998;82(11):2256-61.

144. Panteleakou Z, Lembessis P, Sourla A, Pissimissis N, Polyzos A, Deliveliotis C, and Koutsilieris M. Detection of circulating tumor cells in prostate cancer patients: methodological pitfalls and clinical relevance. Mol Med. United States; 2009;15(3-4):101-14.

145. Bluemel C, Krebs M, Polat B, Linke F, Eiber M, Samnick S, Lapa C, Lassmann M, Riedmiller H, Czernin J, Rubello D, Bley T, Kropf S, Wester HJ, Buck AK, and Herrmann K. 68Ga-PSMA-PET/CT in Patients With Biochemical Prostate Cancer Recurrence and Negative 18F-Choline-PET/CT. Clin Nucl Med. United States; 2016;41(7):515-21.

146. Einspieler I, Rauscher I, Düwel C, Krönke M, Rischpler C, Habl G, Dewes S, Ott A, Wester HJ, Schwaiger M, Maurer T, and Eiber M. Detection Efficacy of Hybrid (68)Ga-PSMA Ligand PET/CT in Prostate Cancer Patients with Biochemical Recurrence After Primary Radiation Therapy Defined by Phoenix Criteria. J Nucl Med. United States; 2017;58(7):1081-1087.

147. Dasgupta A, Lim AR, and Ghajar CM. Circulating and disseminated tumor cells: harbingers or initiators of metastasis? Mol Oncol. United States; 2017;11(1):40-61.

148. Christiansen JJ, and Rajasekaran AK. Reassessing epithelial to mesenchymal transition as a prerequisite for carcinoma invasion and metastasis. Cancer Res. United States; 2006;66(17):8319-26.

149. Arya M, Bott SR, Shergill IS, Ahmed HU, Williamson M, and Patel HR. The metastatic cascade in prostate cancer. Surg Oncol. Netherlands; 2006;15(3):117-28.

150. Liotta LA, Saidel MG, and Kleinerman J. The significance of hematogenous tumor cell clumps in the metastatic process. Cancer Res. United States; 1976;36(3):889-94.

151. Riethdorf S, Fritsche H, Müller V, Rau T, Schindlbeck C, Rack B, Janni W, Coith C, Beck K, Jänicke F, Jackson S, Gornet T, Cristofanilli M, and

Pantel K. Detection of circulating tumor cells in peripheral blood of patients with metastatic breast cancer: a validation study of the CellSearch system. Clin Cancer Res. United States; 2007;13(3):920-8.

152. Thalgott M, Rack B, Maurer T, Souvatzoglou M, Eiber M, Kreß V, Heck MM, Andergassen U, Nawroth R, Gschwend JE, and Retz M. Detection of circulating tumor cells in different stages of prostate cancer. J Cancer Res Clin Oncol. Germany; 2013;139(5):755-63.

153. Berg A, Berner A, Lilleby W, Bruland ØS, Fosså SD, Nesland JM, and Kvalheim G. Impact of disseminated tumor cells in bone marrow at diagnosis in patients with nonmetastatic prostate cancer treated by definitive radiotherapy. Int J Cancer. United States; 2007;120(8):1603-9.

154. van den Bos W, Muller BG, de Bruin DM, de Castro Abreu AL, Chaussy C, Coleman JA, Finelli A, Gill IS, Gross ME, Jenniskens SF, Kahmann F, Laguna-Pes MP, Rastinehad AR, Simmons LA, Sulser T, Villers A, Ward JF, and de la Rosette JJ. Salvage ablative therapy in prostate cancer: international multidisciplinary consensus on trial design. Urol Oncol. United States; 2015;33(11):495.e1-7.

155. Kim J, Park JS, and Ham WS. The role of metastasis-directed therapy and local therapy of the primary tumor in the management of oligometastatic prostate cancer. Investig Clin Urol. Korea (South); 2017;58(5):307-316.

Chapter 10 Appendix

10.1 Forecast Trial Protocol

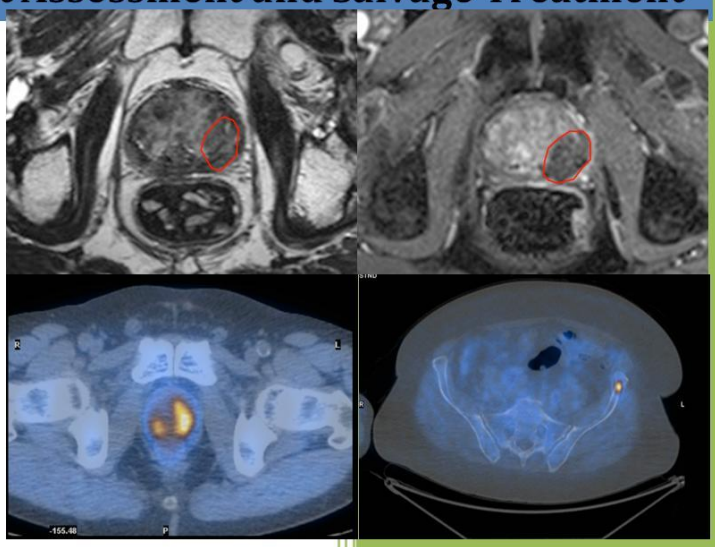
UCL

University College London Hospitals NHS
NHS Foundation Trust

Version 1.3
22nd October 2013

FORECAST

FOcal RECurrent Assessment and Salvage Treatment



Chief Investigator

Hashim Uddin Ahmed

Study coordinator

Abi Kanthabalan

Section 1 Study Outline

1.1 Study title	**FOcal RECurrent Assessment and Salvage Treatment**
Short title	**FORECAST**
1.2 Aim	To evaluate a novel imaging based complex diagnostic and therapeutic pathway intervention for men who fail radiotherapy for prostate cancer
Rationale	Up to one third of men who have radiotherapy for prostate cancer can develop recurrence within 8 years. Half of these men have localised recurrence which may be suitable to local treatment, many are put on expectant management with delayed hormonal therapy that has significant side effects. Focal therapy such as HIFU and cryotherapy has been used as a salvage treatment for radiorecurrent disease with good short term outcomes of oncological control and genitourinary side effects. However in order to provide these focal salvage therapies, recurrent disease must be accurately located and then targeted with focal therapies such as HIFU or cryotherapy.
Study Objectives	**Primary** 1. To evaluate the accuracy of whole-body MRI to detect and rule-out regional lymph node and distant metastatic prostate cancer in men with biochemical recurrence following radiotherapy. 2. To evaluate the accuracy of multi-parametric MRI targeted prostate biopsies in identifying areas of radiorecurrent prostate cancer compared to transperineal template prostate mapping biopsies. 3. To determine the urinary incontinence rate (any pad use) of focal salvage treatment for radiorecurrent prostate cancer. **Secondary** 1. To provide preliminary data to develop and validate novel ultrasound tissue characterisation techniques to detect and rule-out radiorecurrent intra-prostatic cancer compared to transperineal template mapping biopsies. 2. To determine the complications and side-effect profile of focal salvage therapy to treat localised radiorecurrent prostate cancer 3. To provide preliminary data on short term disease control outcomes after focal salvage therapy (PSA kinetics, imaging evidence of localised recurrence, rate of hormone therapy and metastases) 4. To construct a biorepository of imaging datasets with matched primary and metastatic tissue as a future resource for research
Inclusion criteria	1. Previous external beam radiotherapy with or without neo-adjuvant/adjuvant hormone therapy 2. Biochemical failure as defined by the Phoenix criteria (PSA nadir + 2ng/ml) 3. Men considering local salvage treatment for radio-recurrent disease 4. Life expectancy of 5 years or more
Exclusion criteria	1. Have taken any form of hormones (except 5-alpha reductase inhibitors) within the previous 6 months 2. Unable to have MRI scan as defined by standard care practice 3. Metallic implant likely to cause artefact and reduce scan quality 4. PSA doubling time of 3 months or less 5. PSA value 20ng/ml or greater 6. Prior prostate biopsies following biochemical failure 7. Any prior local intervention to the prostate (e.g., laser/electrical resection or incision, cryotherapy, HIFU, any other ablative modality, any other radiotherapy, any other prostate injection therapy for symptoms or cancer control) 8. Unable to have general or regional anaesthesia 9. Unable to give informed consent

Withdrawal Criteria	1. Images are inadequate for analysis due to artefact or image acquisition problems even after a repeat scan 2. Unfit or unwilling to undergo Transperineal Template Prostate Mapping biopsy after undergoing index imaging tests 3. Transperineal Template Prostate Mapping biopsy is inadequate for analysis due to lack of complete gland sampling 4. Unfit or unwilling to undergo focal salvage therapy despite prior eligibility or consent 5. Commencement of hormones at any time-point during study
Study diagnostic procedures	**Standard care** **Distant Disease** Bone Scan Choline PET/CT +/- pelvic lymphadenectomy +/- bone or tissue biopsy **Local Disease** Multi-parametric MRI MRI-Targeted biopsies **Index Tests under evaluation** **Distant Disease** Whole-body MRI **Local Disease** TPM Biopsies
Outcomes and Analysis	**PRIMARY** **Imaging of metastatic disease** **Whole body MRI** lesions suspicious of lymph node, visceral or bone metastases compared to standard care tests - Sensitivity, specificity, negative and positive predictive values of whole-body MRI to detect distant disease compared to standard care tests (isotope bone-scan, PET/CT-scan, with skeletal survey where appropriate) and/or pelvic lymphadenectomy and/or biopsy of distant areas in indeterminate cases **Imaging of Local Disease** **Transperineal multi-parametric MRI targeted biopsies** compared to Template Prostate Mapping biopsies in the detection of UCL definition 2 clinically significant prostate cancer (Gleason >/=3+4 AND/OR Maximum Cancer Core Length >/=4mm in any one biopsy) **Treatment** **Continence**: Presence of urinary incontinence (any pad usage) as determined by the UCLA-EPIC urinary continence questionnaire, at 12 months, in those men with no urinary incontinence at baseline **SECONDARY** **Imaging** **Transperineal multi-parametric MRI targeted biopsies** compared to Template Prostate Mapping biopsies in the detection of clinically significant prostate cancer using a number of target conditions **Treatment** **Serious adverse events and other adverse events** Graded using the National Cancer Institute Common Terminology Criteria (NCI CTC) classification system **Rectal** - Presence of recto-urethral fistula and severe (grade III-type) rectal toxicity - Rate of mild-moderate (grade I-II) rectal toxicity - Presence of new problematic bowel habit at 12 months, as measured by question 9 of UCLA-EPIC Bowel Questionnaire, in those with no previous bowel habit problems

	Continence - Time to return of urinary continence (as determined by UCLA-EPIC Urinary domain questionnaire) - Lower urinary tract symptoms as determined by IPSS and IPSS-QoL scores at 12 months **Sexual** -The presence of severe erectile dysfunction, defined by an inability to have erections sufficient for intercourse, at 12 months, as measured by the IIEF-15 questionnaire with or without the use of phosphodiesterase-5 inhibitors, in those with absence of severe erectile dysfunction at baseline - The presence of any new (mild/ moderate) erectile dysfunction, defined as an at least 6 point drop in the overall IIEF-15 questionnaire at 12 months, with or without the use of phosphodiesterase-5 inhibitors, in those with absence of mild-moderate erectile dysfunction at baseline Rate of PDE5-inhibitor use - Time to return of erectile function (absence of severe ED on IIEF-15 questionnaire) - Change in intercourse satisfaction as measured by intercourse satisfaction domain of the IIEF-15 questionnaire - Change in sexual desire as measured by sexual desire domain of the IIEF-15 questionnaire - Change in overall sexual satisfaction as measured by the overall sexual satisfaction domain of the IIEF-15 questionnaire - The presence of ejaculatory function at 12 months as measured by the orgasmic function domain of the IIEF-15 questionnaire - The presence of orgasmic function at 12 months as measured by the orgasmic function domain of the IIEF-15 questionnaire **Cancer control and disease progression outcomes** - PSA kinetics after focal therapy - Rate of initiating androgen deprivation therapy - Rate of whole-gland therapy - Rate of metastases, overall and disease-specific death
Duration of the study	24 months
Study start date **Study end date**	November 2013 October 2015
Number of subjects	Metastatic Evaluation 177 Localised Evaluation 81 Focal Salvage Therapy 60
Ethics	All subjects must give signed informed consent. Subjects' data will be handled according to regulatory requirements and be protected according to the EU Directive 95/46 EC on data protection as well as local data protection requirements. UK Research Governance guidelines will be adhered to. The protocol must be approved by an independent Ethics Committee and submitted to regulatory agency, if required.

1.3	Contact Details	
Chief Investigator	**Mr Hashim Uddin Ahmed** MRC Clinician Scientist Division of Surgery and Interventional Science University College London 67 Riding House Street London, W1P 7NN	T: 0203 447 9194 F: 0203 447 9303 E : hashim.ahmed@ucl.ac.uk
Co-Principal Investigators	**Professor Mark Emberton** Director, Division of Surgery and Interventional Sciences University College London **Mr Manit Arya** Senior Clinical Lecturer & Honorary Consultant Urologist University College London Hospitals NHS Trust **Dr Shonit Punwani** Senior Clinical Lecturer in Radiology University College London Hospitals NHS Trust	E: markemberton1@btinternet.com E: manit.arya@uclh.nhs.uk E: shonit.punwani@uclh.nhs.uk
Co-Investigator - Study Coordinator	**Dr Abi Kanthabalan** Division of Surgery and Interventional Science University College London	E: abi.kanthabalan@ucl.ac.uk T: 0207 679 9092 F: 0203 447 9303
Co-Investigators – Nuclear Medicine	**Dr Jamshed Bomanji** Consultant in Nuclear Medicine and Head of Department of Nuclear Medicine University College London Hospitals NHS Trust **Dr Athar Haroon** Consultant in Nuclear Medicine University College London Hospitals NHS Trust	E: jamshed.bomanji@uclh.nhs.uk E: athar.haroon@uclh.nhs.uk
Co-investigators – Radiology	**Dr Rowland Illing** Consultant Radiologist University College London Hospitals NHS Trust **Dr Arash Latifoltojar** Radiology Research Fellow University College London Hospitals NHS Trust	E: rowland.illing@uclh.nhs.uk E: arash.latifoltojar@uclh.nhs.uk
Co-investigator - Urology	**Mr Richard Hindley** Consultant Urologist, Basingstoke and North Hampshire Hospitals, Hampshire Hospitals NHS Foundation Trust	E: richard.hindley@hhft.nhs.uk
Co-investigators - Oncology	**Dr Heather Payne** Consultant in Clinical Oncology University College London Hospitals NHS Trust **Dr Anita Mitra** Consultant in Clinical Oncology University College London Hospitals NHS Trust	E: heather.payne@uclh.nhs.uk E: anita.mitra@uclh.nhs.uk
Co-investigators - Histopathology	**Dr Alex Freeman (Lead)** Consultant in Histopathology UCLH NHS Foundation Trust **Dr Charles Jameson** Consultant in Histopathology	E: alex.freeman@uclh.nhs.uk E: charles.jameson@uclh.nhs.uk

	UCLH NHS Foundation Trust	
Co-investigators - Image Registration	**Dr Dean Barratt (Lead)** UCL Centre for Medical Image Computing **Dr Yipeng Hu** UCL Centre for Medical Image Computing	E: d.barratt@cs.ucl.ac.uk E: yipeng.hu@ucl.ac.uk
Co-investigator - Clinical Epidemiology	**Professor Jan van der Meulen** Professor of Clinical Epidemiology	E: Jan.vanderMeulen@lshtm.ac.uk
Co-investigator - Statistician	**Dr Susan Charman** The London School of Hygiene and Tropical Medicine, London	E: scharman@rcseng.ac.uk
Co-investigators - Clinical Trials Unit	**Ms. Chris Brewe-Graves** UCL Clinical Trials Group **Dr Norman Williams** UCL Clinical Trials Group	E: chris.brewe-graves@ucl.ac.uk E: norman.williams@ucl.ac.uk

Sponsor and Trial Site
University College London Hospital

Sponsor representative
Philip Diamond, Joint UCLH/UCL/RFH Biomedical Research Unit. 1st Floor Maple House, 149 Tottenham Court Road, London, W1T 7NF

1.4 Signatures

The Investigators and sponsor have discussed this protocol. The investigators agree to perform the investigation and abide by this protocol except in case of medical emergency or where departures from it are mutually agreed in writing.

Chief Investigator
Mr Hashim U. Ahmed, MRC Clinician Scientist in Urology, UCL

Signature **Date**

Sponsor
Philip Diamond, Joint UCLH/UCL/RFH Biomedical Research Unit. 1st Floor Maple House, 149 Tottenham Court Road, London, W1T 7NF

Signature **Date**

3. Contents

4. Abbreviations and Glossary

MRI	Magnetic Resonance Imaging
Mp-MRI	Multi parametric MRI
DCE	Dynamic Contrast Enhancement
DWI	Diffusion Weighted Imaging
MRSI	Magnetic Resonance Spectroscopic Imaging
TRUS	Trans Rectal UltraSound
PSA	Prostate Specific Antigen
TPM	Transperineal Template Prostate Mapping Biopsy
MCCL	Maximum cancer core length
TCCL	Total cancer core Length
DRE	Digital Rectal examination
PPV	Positive Predictive Value
NPV	Negative Predictive Value
ROI	Region of Interest
UCLH	University College London Hospital

5. Study Summary

5.1 Aim

To evaluate a novel imaging based complex diagnostic and therapeutic pathway intervention for men who fail radiotherapy for prostate cancer

5.2 Rationale

Up to one third of men who have radiotherapy for prostate cancer can develop recurrence within 8 years. Half of these men have localised recurrence which may be suitable to local treatment, many are put on expectant management with delayed hormonal therapy that has significant side effects. Focal therapy such as HIFU and cryotherapy has been used as a salvage treatment for radiorecurrent disease with good short term outcomes of oncological control and genitourinary side effects. However in order to provide these focal salvage therapies, recurrent disease must be accurately located. Currently men undergo a number of imaging investigations (MRI, Choline PET and bone scan) to determine metastatic disease, this is both a burden on the patient and on the NHS. Whole body MRI is a novel imaging technique that has shown to accurately identify distant disease. This imaging technique can replace all three of the above current imaging techniques and also does not depend on radiotracers thus reducing the burden and radiation exposure on patients.

5.3 Objectives

Primary Objectives

1. To evaluate the accuracy of whole-body MRI to detect and rule-out regional lymph node and distant metastatic disease in men with biochemical recurrence following radiotherapy

2. To determine whether multi-parametric MRI targeted prostate biopsies can accurately identify areas of radiorecurrent prostate cancer compared to transperineal template prostate mapping biopsies.

3. To determine the urinary incontinence (pad use) rate of focal salvage therapy to treat localised radiorecurrent prostate cancer.

Secondary Objectives

1. To provide preliminary data to develop and validate novel ultrasound tissue characterisation techniques to detect and rule-out radiorecurrent intra-prostatic cancer compared to transperineal template mapping biopsies.

2. To determine the complications and side-effect profile of focal salvage therapy to treat localised radiorecurrent prostate cancer

3. To provide preliminary data on short term disease control outcomes after focal salvage therapy (PSA kinetics, imaging evidence of localised recurrence, rate of hormone therapy and metastases)

4. To construct a biorepository of imaging datasets with matched primary and metastatic tissue as a future resource for research

5.4 Methods

Men referred to our centre who are suspected to have radiorecurrent disease will be given a patient information sheet on the study before they attend their initial clinic appointment. At this clinic appointment they will be invited into the trial and if they wish to participate, they will be consented into the study and a mpMRI, Choline PET, bone scan and WB-MRI will be performed. If men are found to have metastatic disease, they will be withdrawn from the study. Men with localised disease will proceed to a transperineal prostate mapping biopsy. If the results of the biopsy indicate recurrent cancer that is amenable to focal salvage therapy, they will go on to have focal salvage HIFU or cryotherapy (depending on size and volume of recurrent cancer). They will then be followed up at one month, 3 month, 6 month, 9 month and 12 month intervals where adverse events, PSA and genitourinary function will be recorded.

6. Lay Summary

What are we proposing? We want to ask a number of research questions that might help improve the care of men who have failed radiotherapy for prostate cancer. First, can new types of imaging help us identify those men whose cancer might have spread beyond the prostate? Second, can targeted prostate biopsies to suspicious areas on MR-imaging give us the same information about the cancer and its risk as taking biopsies from the entire prostate in a mapping procedure? Third, what are the side-effects in treating those men who have cancer just in the prostate by targeting the cancer alone (focal salvage treatment) rather than the whole prostate?

Why are we proposing it? Radiotherapy is the most common form of prostate cancer treatment for men in the UK. It is a good treatment. However, 1 in 4 of men will have radiotherapy failure. Most men who experience failure will be offered hormone treatment, either straight away or at some point in the future. A small number are offered re-treatment to their prostate – this is called salvage treatment. In those that have salvage treatment - using surgery or more radiation or by applying heat (HIFU) or ice (cryotherapy) to the prostate - about half the men treated are free from any evidence of cancer at 5 years. We believe there are two reasons for this rather low rate of success. First, the tests we have available - CT scan and bone scan - are not good at telling us whether failure after radiotherapy is due to cancer recurrence in the prostate or disease outside the prostate (metastases). The second reason is due to the difficulty in treating men after radiation. It is technically challenging. Salvage treatments carry a high risk of the side-effects such as incontinence, erection problems, back passage damage. This is because radiation effects are not limited to the prostate and can influence the process of healing in surrounding tissue. The other reason is because the whole prostate is treated even if the cancer is small and limited to one area; damage caused to surrounding tissue is made worse by the salvage treatment. Treating just the cancerous tumour in the prostate only rather than the whole prostate may limit this damage and cause fewer side-effects. This is like a 'lumpectomy' and is called focal salvage treatment. If we could better identify men that had early recurrence with a low probability of cancer outside the prostate, we could offer focal salvage treatment to men most likely to benefit and not treat those men that will gain no benefit.

How are we proposing to do it? We want to test new imaging tests that may help us better identify cancer that has spread outside of the prostate and identify areas of cancer in the prostate more accurately. Our new tests are called whole-body MRI (for distant disease) and multi-parametric MRI guided biopsies (for local disease). Our plan is three-fold. First, we will compare the results of whole-body MRI to existing imaging tests that try to find metastases. Our existing tests are bone-scan, pelvic MRI and choline PET/CT. Second, we will compare the results of prostate MRI-targeted biopsies to a very detailed and accurate biopsy map of the prostate called template prostate mapping which will show us where in the prostate the cancer is and how aggressive it is. Third, if the cancer is confined to the prostate, we will treat men using focal salvage treatment. There are two energies that are currently used to do this called HIFU and cryotherapy. Although HIFU and cryotherapy have been investigated already in men who have had no previous treatment, the evidence for their use as a focal salvage treatment is limited.

What are the expected outcomes? These new imaging tests could better identify those who will benefit from early hormone treatment and better identify those men who will benefit from local salvage treatment and therefore avoid hormone treatment. Our study may help justify carrying out a larger trial looking at how good the treatment is in controlling cancer in the medium and long-term.

7. Background

About 9,000 men with prostate cancer undergo external beam radiotherapy in the UK. One in four will experience biochemical failure. The current pathway fails many of these men by virtue of imprecision in the following two areas: a failure to rule-out metastatic prostate cancer and a failure to rule-in clinically significant residual or recurrent disease within the prostate. This leads to unnecessary treatment in many and delayed treatment in some.

Failure is defined as a PSA rise after radiotherapy of 2ng/ml above the nadir PSA dated at the time of identification (the Phoenix definition)[1]. There are a few challenges associated with PSA rise after radiotherapy. Firstly, a PSA rise does not indicate whether this is due to local recurrence or widespread systemic disease. It may also be a 'PSA bounce': this is a common occurrence after radiotherapy and is thought to be due to remaining areas of viable normal glandular tissue inside the prostate after radiotherapy that produce PSA resulting from inflammation rather than residual cancer cells[2 3 4 5]. Secondly, neo-adjvant or adjuvant hormone therapy is often used at the time of radiotherapy. Adjuvant hormone therapy may be continued for several months post-radiotherapy and therefore it is difficult to estimate what the true nadir is and whether any rises are suppressed by the hormone therapy.

Most men who fail radiotherapy undergo expectant management with delayed androgen deprivation therapy (ADT). ADT has known toxicities such as hot flashes, breast tenderness/enlargement, lethargy; osteopenia, osteoporosis; cognitive impairment; and metabolic syndrome[6]. The commencement of ADT initiates cellular events in the prostate cancer which leads to castrate resistance after a median of 2-3 years. Castrate resistance, when it occurs, triggers a cascade of further costly medication which have variable efficacy rates and toxicity profiles[7 8 9 10 11 12].

The reason for expectant management with delayed ADT being the current standard of care for radiorecurrent prostate cancer is two-fold. Firstly, at least 50% of these men have micro-metastatic disease which is often missed on current staging imaging. These metastatic deposits tend to declare themselves with time making local salvage therapy potentially futile. Secondly, local salvage therapies such as radical prostatectomy, cryotherapy, brachytherapy and high intensity focused ultrasound (HIFU) currently target the whole prostate rather than the cancer area alone. This means that the impact on functional status is significant with most men losing their erections and 30-60% becoming incontinent (if they had retained these functions after radiotherapy). In addition, men can suffer from the catastrophic complication of a recto-urethral fistula (11% to 41%) or rectal injury (2% to 10%) which can require major reconstructive surgery[13].

Trials in men who have had no prior treatment have shown that targeting just the areas of cancer with a margin of normal tissue (using HIFU and cryotherapy) reduces damage to other structures such as neurovascular bundles, external urinary sphincter, bladder neck and rectum. This has led to lower rates of genito-urinary and rectal side-effects with encouraging early to medium cancer control rates[14].

As a result of the problems described above, any innovation in treating men who have failed radiotherapy requires a consideration of the entire pathway, in a manner that we would describe as a 'complex intervention' as defined by the Medical Research Council (MRC) guidelines. In this scenario, we are trying to evaluate the optimal diagnostic and therapeutic interventions to transform the care of men who have failed radiotherapy. These interventions are inter-related and sequential with a number of additional elements of complexity for each test. Furthermore, our study will conform to the IDEAL guidelines for evaluating surgical innovation in a phased manner – our study represents stage 2a of those guidelines (prospective development study) – which were mirrored on the MRC guidelines. The MRC guidelines specifically state that "*Developing, piloting, evaluating, reporting and implementing a complex intervention can be a lengthy process. All of the stages are*

important, and too strong a focus on the main evaluation, to the neglect of adequate development and piloting work, or proper consideration of the practical issues of implementation, will result in weaker interventions, that are harder to evaluate, less likely to be implemented and less likely to be worth implementing." [15]

Current role of imaging in radiorecurrent prostate cancer

The current recommended standard for men who fail radiotherapy is that only those suitable and willing for local salvage therapy undergo further imaging and biopsy. This is nested within only a few centres in the UK. At University College London, for instance, men undergo a staging bone-scan, choline PET/CT and pelvic/prostate multi-parametric MRI as standard care. If localised disease is demonstrated, they undergo a template prostate mapping biopsy of the whole prostate under general/regional anaesthetic in order to prove the cancer is present in the prostate and then to 'map' the cancer for treatment planning. These represent patient and healthcare burdens which could be reduced with fewer imaging tests and fewer better biopsies.

Distant Disease

Radioisotope Bone-scan

After primary treatment of prostate cancer, bone is the first site of relapse in more than 80% of cases[16]. Plain film radiography and radioisotope bone-scans form the mainstay of detection. Bone-scans are more favourable than plain film radiography in diagnosing metastatic disease as they can detect a 10% change in bone mineral turnover, whereas the bone must demineralise by 50% before a lesion is detected by plain film. It can also detect bone metastases up to 18 months before plain film reveals them[17]. Bone-scan and plain film have been shown to underestimate true incidence of metastatic disease. In one autopsy series of 1,589 men with prostate cancer (47% were unsuspected) the incidence of metastatic bone disease was 90%[18]. Bone scan is also well known for its high rate of false positives such as degenerative change, inflammation, Paget's disease and trauma. Other limiting factors are the lack of anatomical detail.

Choline PET/CT

In recent years, both the PET and the CT components of PET/CT technology - including computer hardware and integrated software - have been greatly improved[19]. In addition, it is now possible to perform a contrast-enhanced CT scan in conjunction with PET scanning in the same exam session. In parallel to technological improvements, a significant development in PET radiopharmaceuticals has occurred. Several radiotracers able to visualise different aspects of tumour metabolism are currently available, including 18F-FDG fluorodeoxyglucose for glucose metabolism, carbon 11(11C)/fluorine 18 (18F)–labelled choline (choline) increased cell membrane phospholipid turnover, and 11C-acetate for lipid metabolism, 11C-methionine for amino acid metabolism, and deoxy-18F-fluorothymidine for cell proliferation. In addition, PET tracers capable of imaging specific biologic aspects of cancer tissue are also accessible, including those for hormonal receptor status (e.g., 18F-fluorodihydrotestosterone); for hypoxia (e.g., 18F-labelled fluoroazomycin arabinoside) and 64Cu-diacetyl-bis [N4-methylthiosemicarbazone]); and for tumour angiogenesis (e.g., 18F-arginine-glycine-aspartic acid peptide)[20].

Among the different PET tracers evaluated for prostate cancer imaging, 11C/18F choline has been particularly investigated. It is used for restaging prostate cancer patients[21]. Choline is an essential component of phospholipids of the cell membrane. Cell proliferation and up-regulation of choline kinase are two mechanisms suggested for the increased uptake of this tracer in prostate cancer[22]. The presence of choline transporters also seems to be involved in the process of its uptake in cancer cells[23]. In patients radically treated by EBRT, residual prostate tissue is usually still viable[24]. So the presence of post-EBRT residual viable benign prostate tissue may be responsible for an increased choline uptake at that site as well as malignant prostate tissue[25]. However, the uptake may be different between the two and has been poorly investigated.

Whole-body MRI

Whole-body multi-parametric MRI (WB-MRI) may provide an optimal solution. Recent advances in MRI have made it possible to image the whole body within a reasonable time of about 60 minutes. This enables the study of extra-skeletal involvement, including lymph nodes and other soft-tissue metastases[26 27]. Also WBMRI is conducted without irradiation – a significant advantage considering modern radioprotection[28]. The cumulative irradiation of bone-scan, plain film radiography, and CT generate a dose effectively representing more than several years of natural background irradiation[29].

A few studies have reported good sensitivity and specificity of WB-MRI compared with current imaging tools. LeCouvet compared DWI-WBMRI with BS/plain-films and CT in 100 patients; 68 were felt to have metastases. The sensitivity of BS/plain-films and WB-MRI for detecting bone metastases was 86% and 98–100%, respectively ($p<0.04$), and specificity was 98% and 98–100%, respectively. The sensitivity of CT and WB-MRI for detecting enlarged lymph nodes was similar, at 77–82% for both; specificity was 95–96% and 96–98%, respectively. The sensitivity of the combination of BS/plain-films plus CT and WB-MRI for detecting bone metastases and/or enlarged lymph nodes was 84% and 91–94%, respectively ($p=0.03–0.10$); specificities were 94–97% and 91–96%, respectively. [29]

Another study compared the detection rate of metastatic disease by WB-MRI to BS in 39 patients diagnosed with local prostate cancer. Interestingly, the sensitivity for detection of skeletal metastases for both BS and WB-MRI were 70% (95% CI 0.42–0.98), the specificity 100% and the positive predictive value 100%. WB-MRI and BS differed in the areas of detection. For instance, seven patients had bone metastases on BS and seven had skeletal metastases by WB-MRI, with concordant findings in only four. BS detected more rib metastases, while MRI identified more metastatic lesions in the spine[30]. This study showed that WBMRI and BS have similar specificity and sensitivity but may have to be used as complementary investigations to detect skeletal metastases from prostate cancer, rather than as alternatives.

The recognised limitations of these studies is that histology confirmation was not the reference standard because bone biopsies are not common practice and lymph node dissection is recommended only in patients who are suitable for further salvage therapy. The verification of a negative area is also difficult. In this study, we would perform a bone biopsy if WB-MRI was positive and Choline PET and bone-scan were negative. This decision would be by discussion at a multidisciplinary team meeting. This would ensure that patients who are found to have a negative biopsy and presumed negative for metastatic disease can continue to have focal salvage treatment. If shown to have a better sensitivity and specificity compared to current diagnostic tools used in recurrent prostate cancer, this gives rise to the potential of introduction of WB-MRI as a single test or complementary to one or both of choline PET/CT and bone-scan. This may allow patients to be accurately identified for further treatment appropriately without having the burden of a number of scans and without exposure to further irradiation.

Local Disease

Magnetic resonance Imaging

MRI has rapidly evolved over the last two decades. Traditionally, MRI for prostate cancer has been performed with a 1.5-Tesla (1.5T) scanner and endorectal coil. With the introduction of multiple sequences such as diffusion-weighting and dynamic contrast enhancement as well as higher field strengths (3T), and, thus, higher spatial resolution, the endorectal surface coil can be used less frequently, which makes MRI more accessible and acceptable[31 32].

There are various MRI sequences which include T2-weighted, Dynamic Contrast Enhanced (DCE) and Diffusion Weighted Images (DWI). When these techniques are combined, this is

known as multi-parametric (mp) MRI. In DCE, intravenous gadolinium-based contrast agent is administered while sequential images are taken of the prostate using T1-weighted sequences. The contrast produces different enhancement in prostate cancer and benign tissues due to the differential presence of neo-angiogenesis[33]. In DWI, proton diffusion properties within water-containing tissues are used to obtain image contrast. In healthy prostate tissue, the extracellular and intra-ductal water molecules move freely; and thus the apparent diffusion coefficient (ADC) values are high. In prostate cancer, the normal glandular structure of the prostate is destroyed and there is a higher cellular density than healthy prostate tissue, resulting in decreased extracellular space. Therefore, the proton movement is restricted in prostate cancer, and the cancer shows lower ADC values than surrounding, healthy prostate tissue[34 35]. After radiotherapy, prostatic tissue demonstrates diffuse low signal intensity on T2-weighted MR images, with indistinct zonal anatomy and diffuse low T2 signal, which hinder tumour detection.

Kara et al compared the role of DCE-MRI (1.5T MRI) with transrectal ultrasound (TRUS) in the follow-up (18 months from radiotherapy) of 172 patients who were treated with external beam radiotherapy. Using biopsy results as the reference standard, the sensitivity and specificity of TRUS in the detection of tumour recurrence after radiotherapy were 53.3% and 60%, respectively. The sensitivity and specificity of T2W-MRI were 86% and 100%, respectively; the sensitivity and specificity of DCE-MRI were 93% and 100%, respectively. This study showed that DCE-MRI was significantly more accurate than T2W-MRI for the detection of prostate cancer recurrence after radiotherapy[36]. Haider et al also evaluated the role of mp-MRI against sextant biopsy in 33 men. On a sextant basis, DCE-MRI had significantly better sensitivity (72% [21/29] vs. 38% [11/29]), positive predictive value (46% [21/46] vs. 24% [11/45]) and negative predictive value (95% [144/152] vs. 88% [135/153] than T2W-MRI. Specificities were high for both DCE-MRI and T2W-MRI imaging (85% [144/169] vs. 80% [135/169]). There was a linear relationship between tumor diameters on DCE-MRI and the percentage of cancer tissue in the corresponding biopsy core ($r = 0.9$, $p < 0.001$)[37]. However, TRUS biopsy is known to be a poor reference standard compared to whole-mount histology and whole-gland transperineal template prostate mapping (TPM) biopsies so these results must be interpreted with some caution.

Our institution has shown that MRI-targeted biopsies as well as whole-gland TPM-biopsies have shown promising accuracy rates in identifying radiorecurrent disease[38]. One study looking at only 26 men with biochemical failure after EBRT found that there was a similar rate of detection between MRI-targeted biopsies and TPM for clinically significant cancer detection: 84% (22/26 patients) compared to 92% (24/26 patients), respectively[39].

Biopsy in radiorecurrent disease

On biochemical diagnosis of treatment failure, prostate biopsies should always be obtained to confirm the histological diagnosis of prostate carcinoma if salvage treatment is being considered[40].

TRUS Biopsy

The standard of care for men deemed to be at risk of recurrent prostate cancer is to have TRUS biopsies. There are several important problems with TRUS biopsy and reasons why TRUS guided biopsy would serve as a poor reference test especially in radiorecurrent disease:

1. TRUS biopsies have a false negative rate of up to 30%[41].
2. They systematically under sample the anterior, the midline and the apical parts of the prostate.
3. The deployment of the biopsy needle is tangential (neither sagittal nor transverse), so it is difficult to attribute any sample to any particular location within the prostate.
4. It is difficult to distinguish between radiation-induced atypia of benign glands from malignancy resulting in false-positives. Tumour resolution after radiotherapy has no

identifiable glandular morphology and these remnants can be given a high Gleason score[42] [43] [44]. Poor representation of tissue may be a contributory factor with TRUS biopsies.

Radical Prostatectomy Whole-Mount Step Sectioned Histology

Most men will not be undergoing radical prostatectomy, thus making radical prostatectomy an unsuitable reference test, subject to considerable selection bias. Therefore, an alternative reference test is required that more closely represents the men who would undergo a diagnostic procedure, such as the imaging tests that we will evaluate in this study.

Transperineal Template Prostate Mapping Biopsy

The reference test that closely meets the required specification for our defined population is transperineal template prostate mapping (TPM) biopsies. This has shown a sensitivity of 95% and negative predictive value of 95% for clinically significant cancers of volume >0.5cc, >90% for 0.2cc lesions and 76% sensitivity for all cancers[45]. It also has the advantage of assessing the anterior part of the prostate and attributing biopsy cores to a particular location. The side-effect profile of TPM-biopsies is equivalent to that of TRUS biopsy with two differences. It carries a significantly lower risk of infection and urosepsis as a result of the needles not traversing rectal mucosa (<1% vs. 4%). There is a slightly higher risk of self-limiting urinary retention as a result of gland swelling in 5%-10% of men (compared to 1% risk from TRUS-biopsy)[46]. However, as radiated prostate glands tend to be much smaller than untreated gland, the risk of retention may be lower. The potential disadvantages for the individual man from TPM-biopsies are a general/regional anaesthetic and the risk of over-detection of insignificant cancer. The advantages for the individual man are a reduced infection rate, avoidance of discomfort and pain during the procedure, and greater certainty in risk stratification of recurrent cancer (Gleason grading, tumour burden and location).

Image-fusion/registration

Image-fusion is the process of combining multiple images from various sources into a single representative image. Image-fusion requires image registration - which is a process of mapping equivalent points from different imaging studies so that they correspond. Standard ultrasound is not as good as MRI in differentiating between normal prostate and tumour; however ultrasound is the imaging modality used to guide most biopsy strategies.

Biopsies are therefore currently either taken according to a predefined strategy, within anatomical zones or are targeted based on knowledge of previous biopsies or of other imaging modalities such as MRI.

Image fusion/registration using computer software is being developed with the aim of superimposing an MRI image of a tumour taken prior to biopsy onto a real time ultrasound image so that the tumour focus can be more accurately targeted during the biopsy procedure.

A challenge that presents itself when performing image registration for prostate biopsies is the deformation - change in shape that occurs to the prostate when an ultrasound probe is introduced into the rectum and also when biopsies are taken due to swelling. To address the issue of deformation a novel "model-to-image" registration method by our group has been developed that allows automatic registration of the deformable prostate model surface to the TRUS images[47]. Currently, this registration method does not account for the deformation from gland swelling, only probe distortion. However, work is in progress to assess and compensate for the swelling caused by prostate biopsy and incorporate this into the registration. Image-registration may also improve the delivery of focal salvage therapy by defining the boundaries of the tumour more accurately and thus improve cancer cell kill whilst minimising tissue kill of surrounding areas.

Salvage Ablative Therapy

HIFU in radiorecurrent disease

HIFU works by focusing and depositing a large pulse of high-energy ultrasonic waves on a single area, thereby increasing the temperature to a point whereby, it causes coagulative necrosis. Focused ultrasound waves are emitted from a transducer and are absorbed in the target area of approximately 3x3x10mm of tissue. The result is a targeted thermal effect without damage to the tissue in the path of the ultrasound beam. Two commercially available devices exist for HIFU therapy: Ablatherm (Edap- Technomed, Lion, France) and Sonablate 500 (Focus Surgery, Indianopolis, IN, USA). This study will use the Sonablate 500 device, which has a combined therapy-imaging transducer of different focal lengths, allowing precise control of energy delivery by each pulse. International results show no cancer detected in between 87-94% of men biopsied after whole-gland ablation. Our own results have shown that we can ablate prostate cancer effectively in a whole-gland and focal manner.

Whole-gland HIFU: A small number of studies have looked at HIFU as a potential salvage therapy for radiotherapy failure cases. Murat et al[48] treated 167 patients who had radiorecurrent disease with salvage HIFU. Patients were separated into for low-, intermediate- and high-risk groups and the progression-free survival rate at 3-years was reported as 53%, 42% and 25%, respectively. Ahmed et al had 1- and 2-year progression-free survival rates of to 62% and 48%, respectively, in patients who achieved a PSA nadir of <0.5 ng/ml[49]. Overall, common complications include incontinence (10% to 50%), bladder neck stenosis (17%), retention due to urethral stricture (17%), erectile dysfunction 66.2-100% and recto-urethral fistula (3% to 16%)[50 51 52].

Focal salvage HIFU: There is some data on the role of HIFU as a focal salvage therapy. Our group performed focal salvage HIFU in 39 with disease recurrence confirmed by mpMRI and either 5mm transperineal biopsies (20 men) or TRUS-biopsies (19 men)[53]. Those patients with recurrence confirmed by TRUS biopsies underwent hemi-ablation. Focal salvage therapy was either hemi-ablation (ablation of the lobe up to urethra) or quadrant ablation (ablation of 1 half of the lobe anterior or posterior). If there was multifocal cancer, then the patient underwent index lesion ablation if the untreated areas harboured no more than 1 core with ≤3 mm of 3+3 disease (on TPM) and/or no lesion on mp-MRI. Median follow-up was 17 months (IQR 10-29). Pad-free, leak-free continence status after treatment was 64% and the pad-free rate was 87% as measured at last follow-up using the UCLA Urinary Continence domain questionnaire. Erectile function worsened as IIEF-5 scores decreased from a median of 18 to 13 at 6 months. 23% developed Clavien 3b complications and one developed a recto-urethral fistula although this resolved spontaneously after 6 months of supra-pubic catheter drainage and colostomy, as confirmed on repeat serial MRI studies, urethrograms, and clinical symptoms.

44% of men achieved a PSA nadir of <0.5ng/ml and the 1-year and 2-year biochemical-free survival rates were 86% and 75%, respectively as defined by Phoenix criteria. For men who did not achieve PSA nadir <0.5ng.ml (56%) the 1-year and 2-year biochemical-free survival rates were much lower at 55% and 24%, respectively Phoenix criteria. This study was limited by its retrospective nature, heterogeneity of interventions, its wide and open eligibility criteria and incomplete patient reported outcomes.

Cryotherapy in Radiorecurrent disease

Cryotherapy involves the ablation of tissue through the induction of extremely cold tissue temperatures. Argon is now used to rapidly freeze tissue and exchanged for helium to rapidly thaw tissue. This causes cellular damage and apoptosis. The mechanism by which cellular damage and apoptosis occurs is multi-factorial[54]. During the process of freezing, there is direct cellular damage caused by dehydration, ice crystal formation, and disruption of the cell membrane. Another contributing factor is vascular injury and stasis of blood flow, which then leads to ischemia and necrosis[55 56].

Whole-gland salvage cryotherapy: A number of studies have used whole-gland salvage cryotherapy in radiorecurrent disease, and report good 5-year biochemical disease free rates (40%-58%), which can be go up to 73% in low-risk cases. It must be noted that these studies vary on their definition of biochemical recurrence (PSA >0.5ng/ml or ASTRO or Phoenix definition)[57 58 59 60]. With improvements in technique and development of cryotechnology such as thermocouples that monitor the temperature at important sites within the prostate, and a urethral warming device used to prevent tissue sloughing, complication rates have improved: incontinence 4-73%, recto-urethral fistula 0-3.4%, perineal pain 5.6–39.5% and urinary retention 0–67%[57 58 61]. Sloughing and urethral stricture rates have been reduced from 10–15% to as low as zero[62]. Erectile dysfunction has not improved (72-86%) which patients may already have had as a result of their initial radiotherapy[63].

Focal salvage cryotherapy: One small retrospective series of 19 men who had radiorecurrent disease evaluated by TRUS biopsy underwent hemiablation cryotherapy[64]. Median follow-up was 18 months (range, 6-33 months). The biochemical recurrence–free survival rate (according to the American Society for Therapeutic Radiology and Oncology definition) was 89%, 67%, and 50% at 1, 2, and 3 years, respectively. One of 10 patients harbored residual carcinoma on routine follow-up biopsy at 1 year, whereas 50% harboured residual benign prostate tissue. Complications included incontinence (n=1), urethral stricture (n=1), and urethral ulcer (n=1). The study had severe limitations with no validated patient reported outcomes as well as small numbers, lack of prospective recruitment and lack of transparency as to how patients were selected. Nonetheless, this series as well as the focal salvage HIFU series reviewed above demonstrate that the rate of side-effects may be lower than applying treatment to the whole gland alone.

8. Objectives

Research Question: Can we accurately locate and focally treat radiorecurrent prostate cancer?

Our three-fold approach to this question is reflected by our 3 primary objectives.

Primary

1. To evaluate the accuracy of whole-body MRI to detect and rule-out regional lymph node and distant metastatic prostate cancer in men with biochemical recurrence following radiotherapy.

2. To evaluate the accuracy of multi-parametric MRI targeted prostate biopsies in identifying areas of radiorecurrent prostate cancer compared to transperineal template prostate mapping biopsies.

3. To determine the urinary incontinence rate (any pad use) of focal salvage treatment for radiorecurrent prostate cancer.

Secondary

1. To provide preliminary data to develop and validate novel ultrasound tissue characterisation techniques to detect and rule-out radiorecurrent intra-prostatic cancer compared to transperineal template mapping biopsies.

2. To determine the complications and side-effect profile of focal salvage therapy to treat localised radiorecurrent prostate cancer.

3. To provide preliminary data on short term disease control outcomes after focal salvage therapy (PSA kinetics, imaging evidence of localised recurrence, rate of hormone therapy and metastases).

4. To construct a bio-repository of imaging datasets with matched primary and metastatic tissue as a future resource for research.

9. Study design

9.1 Outcomes and Analysis

Primary

1. Imaging of metastatic disease

Whole body MRI lesions suspicious of lymph node, visceral or bone metastases compared to standard care tests.
- Sensitivity, specificity, negative and positive predictive values of whole-body MRI to detect distant disease compared to standard care tests (isotope bone-scan, PET/CT-scan, with skeletal survey where appropriate) and/or pelvic lymphadenectomy and/or biopsy of distant areas in indeterminate cases

2. Imaging of Local Disease

Transperineal multi-parametric MRI targeted biopsies compared to Template Prostate Mapping biopsies in the detection of UCL definition 2 clinically significant prostate cancer (Gleason >/=3+4 AND/OR Maximum Cancer Core Length >/=4mm in any one biopsy).

3. Treatment

Presence of urinary incontinence (any pad usage plus any leakage of urine) as determined by the UCLA-EPIC urinary continence questionnaire, at 12 months, in those men with no urinary incontinence at baseline

Secondary

1. Imaging

Transperineal multi-parametric MRI targeted biopsies compared to Template Prostate Mapping biopsies in the detection of clinically significant prostate cancer using a number of target conditions

2. Treatment

Serious adverse events and other adverse events
- Graded using the National Cancer Institute Common Terminology Criteria (NCI CTC) classification system

Rectal
- Presence of recto-urethral fistula and severe (grade III-type) rectal toxicity
- Rate of mild-moderate (grade I-II) rectal toxicity
- Presence of new problematic bowel habit at 12 months, as measured by question 9 of UCLA-EPIC Bowel Questionnaire, in those with no previous bowel habit problems

Continence
- Time to return of urinary continence (as determined by UCLA-EPIC Urinary domain questionnaire)
- Lower urinary tract symptoms as determined by IPSS and IPSS-QoL scores at 12 months

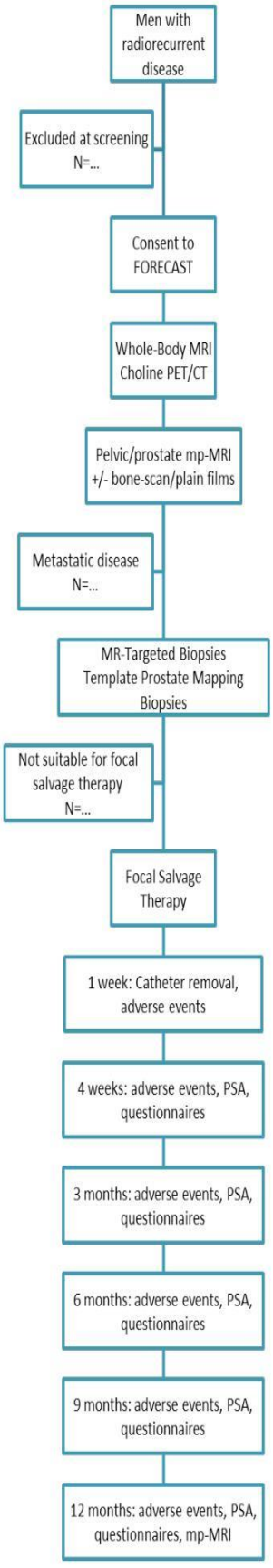
Sexual
- The presence of severe erectile dysfunction, defined by an inability to have erections sufficient for intercourse, at 12 months, as measured by the IIEF-15 questionnaire with or

without the use of phosphodiesterase-5 inhibitors, in those with absence of severe erectile dysfunction at baseline
- The presence of any new (mild/ moderate) erectile dysfunction, defined as an at least 6 point drop in the overall IIEF-15 questionnaire at 12 months, with or without the use of phosphodiesterase-5 inhibitors, in those with absence of mild-moderate erectile dysfunction at baseline
Rate of PDE5-inhibitor use
- Time to return of erectile function (absence of severe ED on IIEF-15 questionnaire)
- Change in intercourse satisfaction as measured by intercourse satisfaction domain of the IIEF-15 questionnaire
- Change in sexual desire as measured by sexual desire domain of the IIEF-15 questionnaire
- Change in overall sexual satisfaction as measured by the overall sexual satisfaction domain of the IIEF-15 questionnaire
- The presence of ejaculatory function at 12 months as measured by the orgasmic function domain of the IIEF-15 questionnaire
- The presence of orgasmic function at 12 months as measured by the orgasmic function domain of the IIEF-15 questionnaire

Cancer control and disease progression outcomes
- PSA kinetics after focal therapy
- Rate of initiating androgen deprivation therapy
- Rate of whole-gland therapy
- Rate of metastases, overall and disease-specific death

9.2 Overall Study Design

The diagnostic pathway evaluation of this study will conform to the STARD (Standards for Reporting of Diagnostic Accuracy) statement. (35) Therefore, the design will ensure that these standards in study design are met from the outset. A number of broad standards can be applied to any diagnostic test (36;37). It will be a single cohort diagnostic study where all participants undergo each of the index tests and the reference test.


Men with radiorecurrent disease
Excluded at screening N=...
Consent to FORECAST
Whole-Body MRI Choline PET/CT
Pelvic/prostate mp-MRI +/- bone-scan/plain films
Metastatic disease N=...
MR-Targeted Biopsies Template Prostate Mapping Biopsies
Not suitable for focal salvage therapy N=...
Focal Salvage Therapy
1 week: Catheter removal, adverse events
4 weeks: adverse events, PSA, questionnaires
3 months: adverse events, PSA, questionnaires
6 months: adverse events, PSA, questionnaires
9 months: adverse events, PSA, questionnaires
12 months: adverse events, PSA, questionnaires, mp-MRI

11. Subject Selection

Inclusion Criteria
1. Previous external beam radiotherapy with or without neo-adjuvant/adjuvant hormone therapy
2. Biochemical failure as defined by the Phoenix criteria (PSA nadir + 2ng/ml)
3. Men considering local salvage treatment for radio-recurrent disease
4. Life expectancy of 5 years or more

Exclusion Criteria
1. Have taken any form of hormones (except 5-alpha reductase inhibitors) within the previous 6 months
2. Unable to have MRI scan as defined by standard care practice
3. Metallic implant likely to cause artefact and reduce scan quality
4. PSA doubling time of 3 months or less
5. PSA value 20ng/ml or greater
6. Prior prostate biopsies following biochemical failure
7. Any prior local intervention to the prostate (e.g., laser/electrical resection or incision, cryotherapy, HIFU, any other ablative modality, any other radiotherapy, any other prostate injection therapy for symptoms or cancer control)
8. Unable to have general or regional anaesthesia
9. Unable to give informed consent

Recruitment
Recruitment will occur from tertiary referrals as well as the local cancer network. We will include all men who are able to have MRI, CT, TPM-biopsy, focal salvage therapy who meet the eligibility criteria for the study.

No participants will be paid to participate within the study.

As above, patients who have had previous EBRT fulfilling criteria for Phoenix definition of biochemical failure and who are being advised to undergo further evaluation of their prostate cancer will be approached by one of the study team. These men will be sent the ethics committee approved patient information sheet. If they are willing to participate in the study, they will be asked to attend the screening visit. A minimum of 24hrs will be given between the patient given the patient information sheet and approaching them again. Men will be given as much time to think about participation in the study as they need.

12. Study Procedures

Visit 1 - Screening and Consent

- The purpose of the research and the study procedure is explained to the participant
- If the participant is willing to take part in the study, eligibility to enter the study is assessed based on inclusion and exclusion criteria.
- If all study criteria are met, a unique study identifier will be assigned to the participant.
- The participant will be asked to sign the approved study consent form. The original signed consent form will be filed in the investigator's master file, a copy given to the participant and a copy filed in the hospital case notes.
- The screening visit CRF is completed and signed by the investigator.
- The participant is deemed to be recruited into the study and the participant's GP is informed.
- Patients will fill out standardized questionnaires which will include IPSS, IPSS-QoL, IIEF-5, EPIC-Continence Function, EPIC-Bowel Function
- PSA blood test and other blood tests if not carried out in prior 6 weeks

Visit 2 – Further Index Imaging tests

The patient will have then have a series of imaging tests (Choline PET-CT, radio-isotope bone-scan (if not already carried out in the last 6 months), mp-MRI Pelvis/prostate and whole-body MRI. These are likely to be on two separate days as currently happens in standard care. The first imaging day is likely to be on the day of consent and screening to reduce burden. (See Appendix One - SOP Diagnostic Imaging Techniques)

Study diagnostic procedures

Standard care	**Index Tests under evaluation**
Distant Disease	**Distant Disease**
Bone Scan	Whole-body MRI
Choline PET/CT	
+/- pelvic lymphadenectomy	
+/- bone or tissue biopsy	
Local Disease	**Local Disease**
Multi-parametric MRI	MR-targeted biopsies
TPM Biopsies	

MDT Discussion 1

The results of the scans will be discussed in an MDT meeting to decide upon the presence of metastatic disease and whether a bone biopsy or pelvic lymph node dissection is necessary for evaluation and whether these should be recommended to the patient. If there is obvious or extensive metastatic disease and it is felt that is not within the patient's best interest to continue with the trial, he will be withdrawn from the study.

Visit 3 – Operating Theatre for Transperineal Template Prostate Mapping Biopsy

Reference Test: Transperineal Template Prostate Mapping Biopsy

This will be carried out under general or regional anaesthetic. Men may also choose to have the procedure under local anaesthetic with sedation. (See Appendix Three – SOP TPM Biopsy)

Risks from Transperineal template prostate mapping biopsy

Complications and risks from general anaesthetic

- Nausea/vomiting after anaesthetic (less than 1 in 10).
- Most men will have a dry cough for an hour or two and may experience a sore throat for 24 hours. This occurs because a mask and /or tube are placed in the throat during the anaesthetic.
- Minor bruises from intravenous catheters (drips) are common.
- Occasionally extensive bruising, temporary hardening of the vein (phlebitis) or infection can occur from intravenous catheters (1 in 20).
- Death. The known risk of death under anaesthesia in the UK is 1 in 150,000 anaesthetics.

Complications and risks of spinal anaesthetic

- Low blood pressure (1 in 10)
- Itching (1 in 10)
- Difficulty passing urine (urine retention) (1 in 10)
- Headache (1 in 10)
- Nerve damage(1 in 10,000)

Complications from TPM-Biopsies

- Blood in the urine (Haematuria) for up to 48 hours (most men)
- Pain passing urine (Dysuria) for up to 24hrs (most men)
- Blood in the semen (Haematospermia) for up to 3-4 months (most men)
- Blood in the urine requiring admission to hospital with catheter tube drainage and bladder washout (1 in 50)
- Retention of urine requiring a temporary catheter (< 1 in 20)
- Prostatitis (inflammation or infection of the prostate, less than 1 in 100)
- Temporary pain/discomfort in the perineal area (most)
- Temporary problems with erections for up to 6-8 weeks (approximately 20-30%, <4-6 weeks).
- Infection requiring admission and intravenous antibiotics (rare)

These side effects are comparable to transrectal biopsies except for a slightly increased risk of urinary retention (5-10% vs. 1% for transrectal biopsies), however due to the likely small nature of the gland, rates of urine retention are likely to be low.

MDT Discussion Two

After TPM-biopsy, patients will be discussed in our MDT meeting in which the imaging and biopsy results (See Appendix Two – Imaging Reporting and Appendix Four - Histopathological specimen reporting) will be discussed to determine whether focal salvage therapy is still appropriate. Patients who have the following will not be eligible to have focal salvage therapy and thus will be withdrawn from the study and returned to standard care either at UCLH or their referring hospitals:

- Men in whom the TPM-biopsies were inadequate for analysis due to lack of complete gland sampling
- Men unfit to undergo focal salvage therapy subsequent to TPM-biopsies
- Men unwilling to undergo focal salvage therapy
- Bulky bilateral disease that would require whole gland treatment

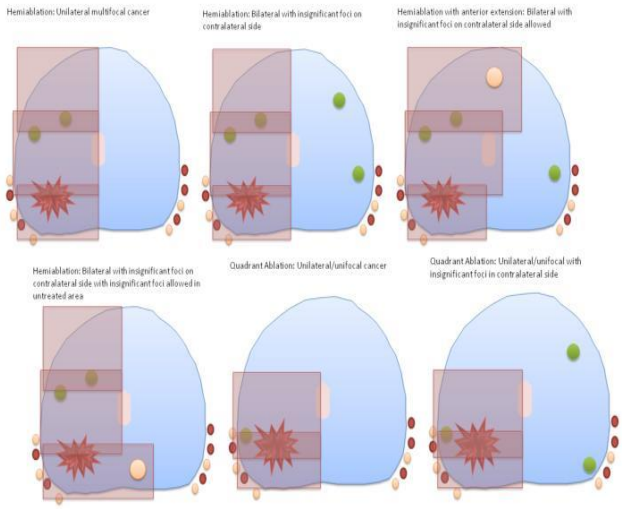
Visit 4 – Treatment

Based on the MDT Discussion patients will undergo either focal salvage HIFU or focal salvage cryotherapy. This is often based on the location of the tumours. Patients are more likely to undergo HIFU if the tumour is posterior and/or apical and men will be advised to have cryotherapy if the tumour is predominantly anterior. The decision in those which are basal-middle and posterior will be pragmatically chosen by physician and patient as would happen in standard care.

Focal Salvage Treatment

The treatment will cover the side of the gland in which the clinically significant lesion(s) have been identified by a combination of MRI and biopsy as follows. (See Appendix Five – SOP Focal Salvage Treatment).The following broad rules will be followed in order to standardise the therapy:

- Tissue will be ablated in the entire affected quadrant of the prostate provided that less than one half of the lobe is affected.
- Treatment will reach the urethra and may cross the midline by up to 5-10 millimeters if the disease is close to the midline (minimum 5mm margin over midline) or crosses over (minimum 10mm margin over midline) (anterior or posterior 'dog-leg'), provided that the treatment does not cross the para-sagittal plane on that side (usually 10mm from midline).
- At least one neurovascular bundle must be avoided by ensuring a minimum distance of ablation zone to contralateral neurovascular bundle of 10mm. This would usually require preservation of the contralateral lobe but the 10mm rule ensures that in patients in whom the dog-leg is used the contralateral neurovascular bundle avoids damage.
- When cancer is seen at the overlapping or going into the apical sphincter on mp-MRI the patient should be excluded.
- In men in whom both lobes meet criteria for clinically insignificant cancer (</=3mm and absence of Gleason pattern 4), the lobe with the dominant disease burden will be treated. This will be evaluated primarily on biopsy results. If these show identical bilateral disease burden, the side with the highest score for probability of malignancy on mp-MRI will be treated. If this is also equivalent, a second review of the biopsies will be requested by the trial pathologist and the dominant side treated. Only those patients with exactly equivalent disease bilaterally following these three reviews will be excluded from the trial. The following diagrams demonstrate the types of treatments that are possible within these rules:



Visit 5 - Catheter removal

- One week after treatment, the supra-pubic catheter withdrawal will occur under antibiotic cover in a clinic setting 7 days after treatment at the treating centre. If the patient fails to void, he will be taught CISC. Failure to void requiring hospitalisation is an expected side-effect of HIFU therapy and will not be reported as a serious adverse event that requires reporting to the sponsor or the Ethics Committee.

Visit 6 – 4 weeks post-treatment

- Telephone consultation or clinic visit to discuss their results and review any adverse events using NCI-CTCAE classification
- Patients reported questionnaires (either posted to them/to fill out in clinic).
- PSA blood test (this can be done at a local laboratory or at investigator site)

Visit 7 – 3 months post-treatment

- Telephone consultation or clinic visit to discuss their results and review any adverse events using NCI-CTCAE classification
- Patients reported questionnaires (either posted to them/to fill out in clinic).
- PSA blood test (this can be done at a local laboratory or at investigator site)

Visit 8 – 6 months post-treatment

- Telephone consultation or clinic visit to discuss their results and review any adverse events using NCI-CTCAE classification
- Patients reported questionnaires (either posted to them/to fill out in clinic).
- PSA blood test (this can be done at a local laboratory or at investigator site)

Visit 9 – 9 months post-treatment

- Telephone consultation or clinic visit to discuss their results and review any adverse events using NCI-CTCAE classification
- Patients reported questionnaires (either posted to them/to fill out in clinic).
- PSA blood test (this can be done at a local laboratory or at investigator site)

Visit 10 – 12 months post-treatment

- mp-MRI to assess for residual disease
- Telephone consultation or clinic visit to discuss their results and review any adverse events using NCI-CTCAE classification
- Patients reported questionnaires (either posted to them/to fill out in clinic).
- PSA blood test (this can be done at a local laboratory or at investigator site)

Study Visits

Summary Table

	Test or intervention									
Study Visit	PSA	Choline PET/CT	Whole-body MRI	Bone-scan	Pelvic/prostate MRI	TPM	MR-targeted biopsies	Focal salvage therapy	Adverse events	Questionnaires
1	X	X	X							
2				X	X					
3						X	X			
4								X	X	
5	X								X	X
6	X								X	X
7	X								X	X
8	X								X	X
9	x								X	X

13. Blinding & other measures taken to avoid bias

Bias

Selection Bias

We will try and minimise any selection bias by approaching all men for trial participation who have undergone EBRT or brachytherapy who have been deemed to have biochemical failure and referred for further evaluation. Recruitment will occur from tertiary referrals as well as the UCL Partners cancer network. We will include all men who are able to have MRI, CT, TPM-biopsy, focal salvage therapy who meet the eligibility criteria for the study.

A prospective screening log of all men approached for consideration of inclusion into the study will be kept, and all men who consented for inclusion but who did not complete the study will be reported.

Importantly, for each comparative analysis (WB-MRI versus standard staging tests; MRI-targeted biopsies and novel ultrasound tests versus TPM-biopsies) all men who are considered likely to benefit from having these tests will have both the index test and reference test relevant for each comparison; this will minimise the selection bias in a manner that reflects the clinical imperative. In other words, if initial tests show evidence of metastatic disease these men will not be included for further tests as it is considered that men with metastatic disease experience more harm from further invasive tests such as TPM-biopsies. This exclusion reflects the clinical standard and thus selection bias is minimised.

Expectation bias

To minimise this bias clinicians reporting WB-MRI and pelvic/prostate mp-MRI will be blinded to the result of the other. They will however have equal access to previous patient details such as PSA, previous biopsy results at initial diagnosis prior to radiotherapy, previous radiotherapy details and use of neo-adjuvant/adjuvant hormones, in order to pragmatically reflect standard practice. In other words, as the study aims to assess the capability of imaging to aid in the normal diagnostic pathway, supplying reporters with relevant patient information is appropriate.

Verification Bias

Patients will remain blinded to the results of the index tests under evaluation until after the appropriate reference test has been conducted. Patients will be excluded from analysis if they are withdrawn from the study or unable to undergo the reference test after one of the index test, or are unable to have focal salvage HIFU.

14. Data collection

Responsibility for data collection will be taken by a nominated individual. Data will be collected in paper form in the first instance. Data will be collected in both electronic and paper form. Data will be stored centrally by the sponsor centre. The data will be reviewed regularly by the TSC. Data 'cleaning' and database entry will also be performed by the trial administrator, with overall supervision and responsibility by the trial manager. An external audit of data will be performed according to standard operating procedures of the sponsor or their delegated body.

Data will be held according to the Data Protection Act 1998 and pseudo-anonymised as necessary. Each participant will be given a study number and this will be used on all of their study records. The patient number will be known to Miss Abi Kanthabalan and the UCL CTG. All clinic visit information including questionnaires, scans, biopsy results and blood results will be kept in study records and analysed at the end of the study. Questionnaires will be sent to all trial patients centrally and the responses kept confidentially at the sponsor centre and access will be available by the relevant trial centre. The records will be kept in a secure manner in the research offices with access available to named individuals from the study group only. All imaging data (MRI and ultrasound) will be held confidentially and processed by the named investigators for the purpose of image registration analysis, including the use of secure computer software for video linked proctoring between sites.

The paper records will be retained for a minimum of 20 years after the end of the study, according to UCL guidelines. Any information that is transferred between trial centres or from general practitioners surgeries will be anonymised.

15. Statistical Plan

Methodological and Statistical considerations
Consecutive prospective recruitment of patients from a clinically relevant population with masked test results will minimize bias and will ensure that the results from this study have clinical applicability. Patients who fulfil the eligibility criteria will be selected so that the study sample has a disease prevalence that is representative of the population of interest. This is particularly important as predictive values depend on the disease prevalence in the population. Both patients and assessors will be blinded to the test results until the index test is completed and reported.

Sample size calculation
Sample size calculations have been undertaken for the 3 co-primary objectives so that robust data can be obtained for each. To detect a proportion of agreement of, pA, between the index test under evaluation and the reference test with 95% CI of =/-5% (error), the following numbers are required.

Primary Objective 1. To evaluate the accuracy of whole-body MRI to detect and rule-out regional lymph node and distant metastatic disease in men with biochemical recurrence following radiotherapy

- pA = 95% with 50% prevalence of metastases
- Minimum N=144 required

Primary Objective 2. To determine whether multi-parametric MRI targeted prostate biopsies can accurately identify areas of radiorecurrent prostate cancer compared to transperineal template prostate mapping biopsies.

- pA=95% with 90% prevalence of disease
- Minimum N=81 (to be biopsied)

Primary Objective 3. To determine the urinary incontinence (pad use) of focal salvage therapy to treat localised radiorecurrent prostate cancer.

Currently, we are able to achieve incontinence rates of approximately 40% (any pad-use) following whole-gland salvage therapy. In order to obtain a precision-based estimate on the rate that focal salvage therapy will give rise to, it is estimated that 20% incontinence (any pad use) may occur. Of the 80 men biopsied, we estimate that three-quarters are likely to be suitable for focal salvage therapy, giving N=60 men treated. This gives a 95% confidence interval of +/-10.1%. If incontinence was slightly lower (15%), then the 95% CI would be +/-9.0%. If incontinence was higher (25%), then 95% CI would be +/-11.0%.

Therefore, it is likely that we will need to recruit N=162 in total but with a 10% withdrawal rate, this is N=177 in order to meet the minimum numbers required for each objective. An interim analysis will be conducted at N=50 and N=100 by an the Data Monitoring Committee and adjustments made to the sample size calculations dependent on disease prevalence at each stage and initial pA rates and errors around these rates If recruitment rate is higher than anticipated then adjustments will be made in light of these by the DMC and recommended to the Trial Steering Committee.

See Appendix Six – Statistical Plan for detailed analysis plan.

16. Compliance and withdrawal

Methods for improving the patient experience, particularly in the treatment of 'chronic' conditions or those that demand frequent hospital attendance, may improve tolerability and adherence to treatments and follow-up investigations. The use of telephone consultations as a means of follow-up has demonstrated good patient acceptability, over a range of medical and surgical specialties and different health-care professionals.

Telephone consultation offers a more convenient, time-efficient, less burdensome and economical alternative to clinic appointments. Furthermore, a reduction in visits across a patient cohort, some of whom are prepared to travel a considerable distance for treatment within a trial, would contribute a small but significant reduction in the carbon-footprint.

Withdrawal Criteria

1. Images are inadequate for analysis due to artefact or image acquisition problems even after a repeat scan
2. Unfit or unwilling to undergo Transperineal Template Prostate Mapping biopsy after undergoing index imaging tests
3. Transperineal Template Prostate Mapping biopsy is inadequate for analysis due to lack of complete gland sampling
4. Unfit or unwilling to undergo focal salvage therapy despite prior eligibility or consent
5. Commencement of hormones at any time-point during study

17. Discontinuation of Study

Study Discontinuation by the Sponsor

The Sponsor may terminate the study at any time if the following occur, and the investigator is unable to take corrective action in any of these cases:

- The investigator is non-compliant with the protocol
- The investigator is non-compliant with the regulatory requirements
- The investigator is non-compliant with the principles of Good Clinical Practice as outlined in the Declaration of Helsinki and the Research Governance Framework (version 2)
- The CRF completion or drug accountability is inadequate

Discontinuation of Study for an Individual Patient

The criteria for discontinuing the study in the case on individual patients are:

Intercurrent illness
Any illness, which in the judgment of the investigators would affect the assessments of clinical status to a significant degree

Request by the patient
It is the patients right to request discontinuation of their participation in the study. If this request is made, it will be respected and will not affect the patient's ability to receive medical care from the investigators now or in the future.

Discontinuation of attendance at an investigating site
Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients no longer attend the participating institution.

18. Quality Assurance

In order to ensure the quality of the data collected in the study, the principal investigator will provide means for data monitoring and QC of the database. Data will be handled according to regulatory requirements and be protected according to the EU Directive 95/46 EC on data protection as well as local data protection requirements.

19. Adverse Event Definitions

Adverse Event
Any untoward medical occurrence in a subject including occurrences, which are not necessarily caused by or related to the intervention

Adverse Reaction
Any untoward and unintended response in a subject, which is related to the intervention

Unexpected Adverse Reaction
An adverse reaction, the nature and severity of which is not consistent with the intervention's applicable product information (investigator's brochure)

Serious Adverse Event/Reaction (SAE/SAR)
Any untoward medical occurrence that:

- Led to a death
- Led to a serious deterioration in the health of the patient, user or others and includes:
    1. A life threatening illness or injury
    2. A permanent impairment to a body structure or function
    3. A condition requiring hospitalisation or increased length of existing hospitalisation (except redo salvage treatment, elective intervention for urethral stricture, hospitalisation for planned admission unrelated to the intervention, urinary retention requiring catheterisation, planned admission for further biopsies at follow-up).
    4. A condition requiring otherwise unnecessary medical or surgical intervention and which might have led to death or serious deterioration in health had suitable action or intervention not taken place. This includes malfunction of the device such that it has to be monitored more closely or temporarily or permanently taken out of service.
- Led to foetal distress, foetal death or a congenital abnormality or birth defect
- Might have led to any of the above

Suspected Unexpected Serious Adverse Reaction
All suspected adverse reactions related to the intervention that is both unexpected and serious

Adverse Events Information Collection

All adverse events regardless of severity or causal relationship with the intervention observed by the Investigator or reported by the patient and occurring during the study period will be recorded in the Case Report Form (CRF). The date of onset, intensity, action taken due to the event, duration, date of resolution of the event, outcome, and relationship to the study intervention will be recorded. The definitions used to describe the relationship between the adverse event and the study interventions are the following:

Unrelated
An adverse event that is definitely not related to the intervention.

Unlikely
An adverse event for which an alternative explanation is more likely e.g. concurrent drug(s), concomitant disease(s), and/or the relationship in time suggests that a causal relationship is unlikely.

Possible
An adverse event that might be due to the intervention. An alternative explanation e.g. concurrent drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be excluded.

Probable
An adverse event that might be due to the intervention. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely e.g. concurrent drug(s), concomitant disease(s).

Very likely
An adverse event, that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation e.g. concurrent drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g. it is confirmed by de-challenge and re-challenge).

Unassessable
It is not possible to assign the reaction to any of the above categories because of insufficient, pending or contradictory information. Further information is requested in order to lead to an attribution of causality.

Serious Adverse Events (SAE) Reporting

All serious adverse events must be reported to the sponsor UCL within 24 hours (via research-incidents@ucl.ac.uk) of the Investigator's knowledge of the event except for those that are identified in the protocol as not needing immediate reporting. The sponsor or Chief Investigator must also notify the Main Research Ethics Committee for the trial within 15 days of the Chief Investigator becoming aware of the event, using the appropriate SAE report form. As the HIFU and cryotherapy device are CE marked medical devices, any Serious Adverse Device Effects (SADE) and any suspected unexpected SADE must also be reported to the MHRA (to the Devices Adverse Incident Centre) and the manufacturer of the device.

Those events arising from all participating centres will be reported on a three monthly basis in a summary format, to include:

- The number of serious adverse events from all participating centres in a tabular format laying out the percentages of each type of serious events with an indication as to how many of those are thought to be device related or non-device related
- The total number of patients recruited during that same 3 month period and in total

Safety
The study is performed on subjects with suspected radiorecurrent prostate cancer.
- The risk of serious adverse events due to MRI, MRI-PET, Choline PET or bone scan expected is low.
- Prostate biopsies performed by transperineal template mapping prostate biopsies have been shown to be safe and the side-effect profile is comparable to standard transrectal prostate biopsies. It carries a lower risk of sepsis and rectal bleeding, but does have a higher risk of temporary urine retention. Alpha blockers are administered to the patient prior to the procedure to minimise this risk. In men in whom this complication does occur a temporary catheter will be placed overnight and removed the following day.
The transperineal template prostate mapping biopsy also requires either a general or spinal anaesthetic although some men can have this under local anaesthetic with sedation.
- More biopsy cores are obtained than at TRUS-biopsy. This does increase the burden on the patient slightly, but patients will benefit from less discomfort at the time of biopsy and more accurate risk stratification of their disease.

Indemnity
The study is sponsored by UCL, which carries indemnity for negligent harm arising from the design of the research.

20. Ethics

The protection of human subjects' rights and well-being will be carried out in accordance with the current version of the Declaration of Helsinki.

Subject Information and Informed Consent: The patient's consent to participate in the study should be obtained after a full explanation has been provided of the procedures to be given. All subjects must sign and personally date an approved informed consent after having received detailed written and verbal information about the reason, nature and possible risks associated with the research program. Patients should be given sufficient time (at least 24 hours) after being given the study patient information sheet to consider and discuss participation in the study with family and friends. Patients will always be asked to sign a consent form. One copy will be given to the patient, one copy will be kept with patient's hospital notes and one copy should be kept in the local investigator's file.

The subject must be made aware and agree that personal information may be scrutinized during monitoring and audit by competent authorities and properly authorized persons. However, personal information will be treated as strictly confidential and will not be publicly available.

The right of the patient to refuse to participate in the study without giving reasons must be respected. After the patient has entered the study, the clinician must remain free to manage the patient however he/she feels fit to suit the best interest of the patient, regardless of the protocol. Similarly, the patient must remain free to withdraw from the study at any time without giving reasons and without prejudicing any further treatment or the standard of care received.

An Institutional Review Board and/or an Independent Ethics Committee must approve the protocol, the patient information sheet, the content of the informed consent form and any promotional materials used for the recruitment of subjects before the accrual of any patients. If legally required, the protocol and informed consent must be submitted to the country regulatory authorities

21. Publication Policy

The results of scientific interest from the study and any parallel translational work, will be submitted for consideration of presentation to professional and scientific meetings, and publications in the peer reviewed professional and scientific literature. They may also be included in theses and dissertations. Any submissions are to have authorisation from the Chief Investigator and Co-Investigators. Authorship will be determined on a per paper basis.

Appendix

Appendix One – SOP Diagnostic Imaging Techniques

Multi-parametric MRI procedure at MRI suite
All MRI's will be performed at UCLH using either a 1.5 Tesla or 3 Tesla scanner and a pelvic phased array receiver, with a pelvic coil. A full protocol of T1 and T2 weighted turbo-spin echo images, diffusion weighted images and a dynamic post gadolinium volume acquisition will be used.

Risks from the Contrast-agent Gadolinium during the MRI Scan
Gadolinium contrast is a solution injected into the vein to make cancers appear more clearly on the MRI. The use of gadolinium is very safe and widely used in clinical practice and not just for this study. Some complications occur and include:
- nausea and vomiting (less than 1 in 2,000)
- mild allergic reaction (e.g., rash, itching) (less than 1 in 250)
- moderate allergic reaction (less than 1 in 2,000)
- severe allergic reactions (breathing problems, face swelling) (less than 1 in 10,000)

Choline PET/CT
Patients will be injected with 300-370 MBq of ^{18}F-FECH. Whole-body PET/CT images will be acquired 60 min after tracer injection. Owing to the rapid excretion of FECH in urine, the patients will be asked to empty their bladder prior to imaging. At approximately 90 min, a limited (one bed position, PET/CT) pelvic view will be obtained with the prostate in the field of view. The CT acquisition parameters include: scout 120 kVp, 10 mA; CT 140 kVp, 80 mA, 0.8 s, pitch 1.75; CT slices 5 mm (70-cm FOV PET AC), 2.5 mm (50-cm FOV Std), 2.5 mm (50-cm FOV Lung). PET acquisition parameters will be: 3D attenuation-corrected and non-attenuation-corrected images, 20 subsets with iterative reconstructions. CT images will be used to produce attenuation correction values for PET emission reconstruction and fused PET/CT presentation.

Bone-scan +/- plain radiography
Bone imaging is used to detect skeletal lesions, monitor the course of skeletal disease and evaluate the metabolic activity of skeletal lesions. Bone scans are performed using Technetium-99m labelled diphosphonates administered through intravenous injection. These diphosphonates chemically bond on the surface of hydroxyapatite crystals on the surface of bone such that the images represent local osteoblastic activity. Metastases, infection, fracture and other bony lesions that cause an osteoblastic response are therefore well detected with bone imaging. For prostate cancer patients with suspected bony metastasis, whole body protocol is being used. Whole body imaging is performed with anterior and posterior views, 256 x 1024 matrix and energy window(s) of 140 KeV. Effective dose (ED) is 3mSv (or 5mSv for Cancer patients) and Diagnostic Reference Level (DRL) is 600 MBq (0r 800 for Cancer patients).

Appendix Two – Imaging Reporting

MRI Prostate reporting

All MRI sequences will be reported by an experienced Uro-Radiologist. They will be blinded to the transperineal template prostate mapping biopsies histology, but clinical details such as PSA, previous biopsy result, previous radiation therapy and use of hormones will be available to them.

The MRI will be scored using a system agreed upon at European consensus meeting for the presence of clinically significant prostate cancer.

The location of each lesion will be displayed diagrammatically, in number and written from using a standardised proforma. This is to identify the number of tumours seen and to give greater meaning to the relationship of the scores in adjacent regions of interest (ROIs). For example, this will allow us to know whether two adjacent regions scoring 5 (high likelihood of cancer) are due to two separate tumours in each region or one tumour encompassing both ROIs. Each of the drawn tumours will be labelled with a letter by the radiologist to again identify continuity of tumours between basal and apical segments. An anonymised copy of the radiology report will be filed in the study folder after the TPM had been performed.

If a tumour is visible on T2 weighted images within the prostate, the patient will have an MRI-targeted biopsy at the time of prostate mapping, based on MRI-US registration. Thus the MRI image/lesion will be delineated and contoured as outlined in Appendix three 'TPM biopsy' below.

Multi Parametric MRI Phasing details for Prostate detection Scan

Sequence	Coil	TR	TE	FA degrees	ETL	BW Hz/Px	FoV mm	Phase FoV %	Slice Thicknes	Gap	NEX	Phasing direction	FS	Matrix base	Matrix phase %
T2 TSE Coronal	Body	5240	104	150	24	190	180	100	3	0.3	2	R>L	No	256	95
ep2d Diffusion b1400	Body	2200	98	0	172	968	320	100	5	0	32	A>P	Yes	172	100
ep2d Diffusion new 16	Body	2100	96	0	172	968	260	100	5	0	16	A>P	Yes	172	100
T2 axial tse trs 3mm	Body	5170	92	180	22	191	180	100	3	0.3	2	A>P	No	256	100
T1 Flash 3d match VIBE	Body	10.4	4.78	15	0	130	260	100	3	0.6	1	A>P	Yes	256	100
T1 VIBE 5degrees	Body	5.61	2.5	5	0	300	260	100	3	0.6	1	A>P	Yes	192	100
T1 VIBE 20degrees	Body	5.61	2.5	20	0	300	260	100	3	0.6	1	A>P	Yes	192	100
T1 VIBE 10degrees	Body	5.61	2.5	10	0	300	260	100	3	0.6	1	A>P	Yes	192	100
T1 VIBE 25degrees	Body	5.61	2.5	25	0	300	260	100	3	0.6	1	A>P	Yes	192	100
T1 VIBE 15degrees perfusion 35 mea	Body	5.61	2.5	15	0	300	260	100	3	0.6	1	A>P	Yes	192	100

MRI Reporting Proforma

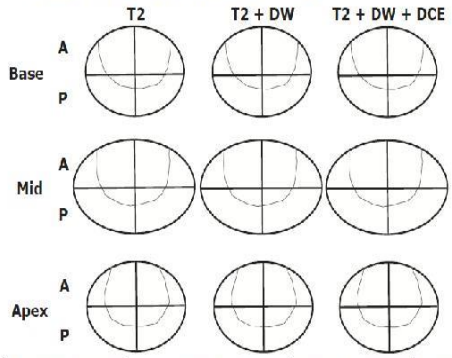
Patient's Initials: | Date of Birth: d d m m y y y y | Trial Number:

Hospital Number: | Scan Date: d d m m y y y y | Reporter: *(Please tick)* **Local** ☐ / **Central** ☐

1. SIZE OF PROSTATE

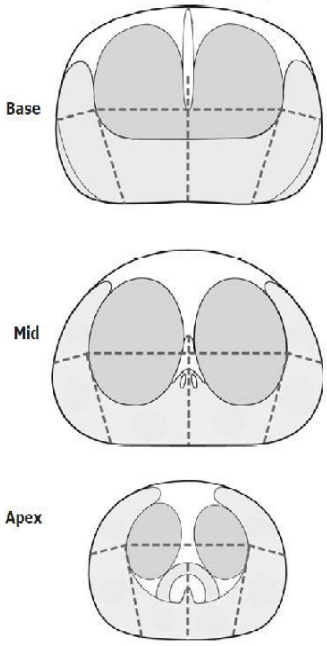
Transverse	Anterior-Posterior	Cranio-Caudal	Volume
* cm	* cm	* cm	cm³

2. SECTOR *(Please report strictly in order on the diagram below, please put a value 1-5 (MRI Score†) in each Region of Interest)*
P = Posterior 1.7cm (Measured from posterior capsule)



Risk category	Disease Threshold	Overall MRI Score† (1-5)
Any cancer	Any Disease	
Definition Two	≥ 0.2cc and/or ≥ 3 + 4	
Definition One	≥ 0.5cc and/or ≥ 4 + 3	

3a. INDIVIDUAL LESIONS *(Please draw and number measurable lesions on diagram below)*



3b. INDIVIDUAL LESIONS
(Using the lesions drawn in 3a please score each lesion on the table below)

Lesion No.	T2	D	C	All	Likely co-ordinates** (2 most likely)		Curve 1=Slow rise 2=Iter 3=Early peak	ADC	Zone	Max diameter	Volume	Distance from posterior capsule	Estimated Gleason Grade	Estimated Cancer Significance
	MRI Score† (1-5)						1-3	Value	PZ/TZ/both	mm	cc	mm	e.g. 3+4	Not Sig/Del 1/Del 2
1														
2														
3														
4														
5														
6														

** x,y grid coordinate 1° apex (a) or base (b) e.g. b2.5a, C2.5a, E1.5b (lower case underlined for 'c').

4. STAGING

	Vesicles involved?	Extra-capsular?	Sphincter (T4)?	Rectum (T4)?	Nodes?
MRI Score† (1-5)					
If score >2, Left or Right?					

If score for nodes > 2, max short axis nodal diameter? ☐☐ (mm)

†MRI Score
1=Highly likely benign
2=Likely benign
3=Equivocal
4=Likely malignant
5=Highly likely malignant

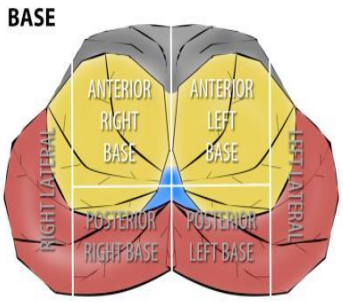
Signature:	Author Name:	Report Date: d d m m y y y y

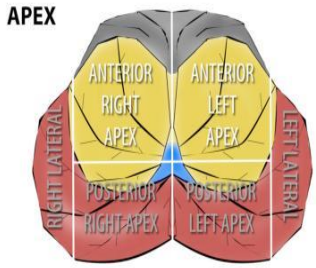
Bone Scan and Choline PET/CT reporting

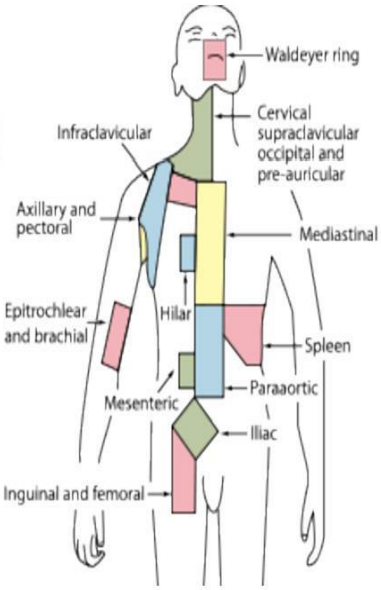
All bone scan and choline PET sequences will be reported by a Nuclear Medicine Consultant. They will be blinded to the transperineal template prostate mapping biopsies histology, but clinical details such as PSA, previous biopsy result, previous radiation therapy and use of hormones will be available to them.

Bone Scan Reporting Proforma

Choline PET Reporting Proforma







Appendix Three –TPM-BIOPSIES

Pre-operative preparation

This is a day case procedure. The patient will be admitted on the morning of the procedure. In order to reduce the risk of urinary retention, men will be given an alpha-blocker (alfuzosin XL 10mg once daily or tamsulosin 400mcg once daily) to start AT LEAST 3 days prior to transperineal template prostate mapping biopsy unless they are on an alpha-blocker already. The patient will be asked to sign the hospital informed consent form. The procedure is performed under general anaesthesia or spinal anaesthesia.

Procedure set-up

Intravenous antibiotics (Gentamicin 120mg and Cefuroxime 1.5gm) are given at the time of induction unless contra-indicated. The patient is placed in the lithotomy position, the perineal skin is prepared and draped and a urethral catheter is inserted and spigotted. This helps to identify the urethra and is used as a baseline reference point.

A transrectal ultrasound probe with an inflatable endocavity balloon is mounted onto a specifically designed stepper and the probe is gently introduced in to the rectum. Once the prostate is well visualized, the position of the probe is fixed. Then the disposable 5mm spaced brachytherapy template is mounted onto the stepper and is placed against the perineum to guide biopsy needles into the prostate. 20mls of local anaesthetic is infiltrated into the perineal skin (Marcaine 0.5% with adrenaline 1/200,000units) to minimise bleeding and discomfort.

Figure 1: Method used for Transperineal template prostate mapping biopsies

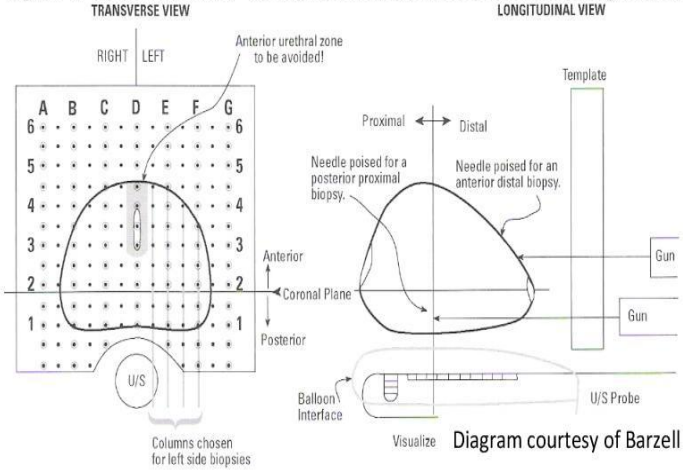


Diagram courtesy of Barzell et al (1)

Biopsy procedure

Prior to the standard transperineal template prostate mapping biopsy the targeted samples will be obtained. The coordinate of the first biopsies taken will be based on the location of the tumour identified by the radiologist on mpMRI. The operator will attempt to target the tumour using this 'cognitive registration' method. This biopsy core will be placed in its own cassette and labelled as 'MRI cognitive registration targeted biopsy 1' and the XY co-ordinate used given. A second biopsy core to this suspicious lesion will be permitted- 'MRI cognitive registration targeted biopsy 2", this will be placed within the same cassette. In those patients with an MRI-visible tumour, the coordinate of the third pair of biopsies will be based on the MRI to US computed fusion/ registration process, whereby the image of the tumour location on MRI will be superimposed onto the real-time US image. The maximum number of targeted cores that will be taken is four. Following these targeted biopsies, a systematic biopsy of the whole prostate using the 20 modified Barzell zones *(appendix 5)* will

be undertaken. Biopsies are taken with a 20mm core biopsy needle with 2 biopsies from each of 20 Barzell zones, guided by a template brachytherapy grid.
Through each chosen co-ordinate of the template, the needle is deployed from the apical edge of the prostate up to the mid-gland to obtain the apical core and likewise from the mid-gland to the base to obtain the basal core except, at the lateral aspects where a single biopsy will be sufficient due to the short z-axis of the prostate in its outer limits.
Biopsies are obtained for each modified Barzell zone (*see appendix 5*) then placed in a histology cassette for that zone.

Post-operative care
At the end of the procedure the catheter is removed. The patient is discharged home once he has voided urine satisfactorily. A prescription for analgesia is given. Alpha blockers are continued for a minimum of a week after the procedure. A contact number is given to the patient to call if any problems are encountered. Patients will also be asked to fill an online IPSS questionnaire, 4 weeks after the biopsy.

Storage and Access of Biopsy Samples
All tissue samples will be held according to UCLH Histopathology Departments NHS Standard Operating Procedures. No additional tissue will be taken for the purpose of this study. Members of the clinical team involved in the patients care will have access to these results.

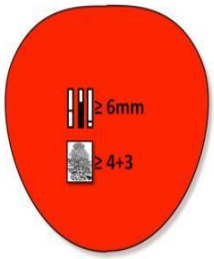
Appendix Four - Histopathological specimen reporting:

The following information is reported for each biopsy core:

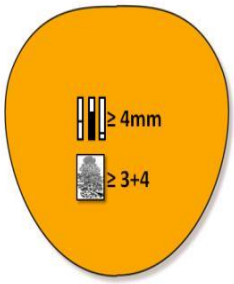
- Total Core length
- Presence or absence of cancer
- Cancer core length
- Gleason grade
- Percentage of pattern 4 per core where relevant

The sectors are labelled according to zone 'Appendix Four – Barzell Zones'. This will serve to generate a 3-dimensional model that demonstrates the presence or absence of prostate cancer at 5mm intervals. The transperineal template prostate mapping biopsy results will then be grouped into 20 regions and each histological region will be scored using a risk classification system, for low, intermediate and high risk cancer. A histological report will be produced and an anonymised copy of the histological report will be filed in the study folder.

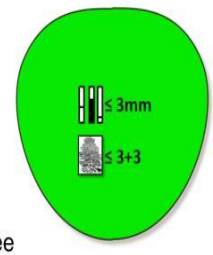
The definitions of clinical significance of prostate cancer vary, for the purpose of our study the following definitions will be used:



Definition one



Definition two

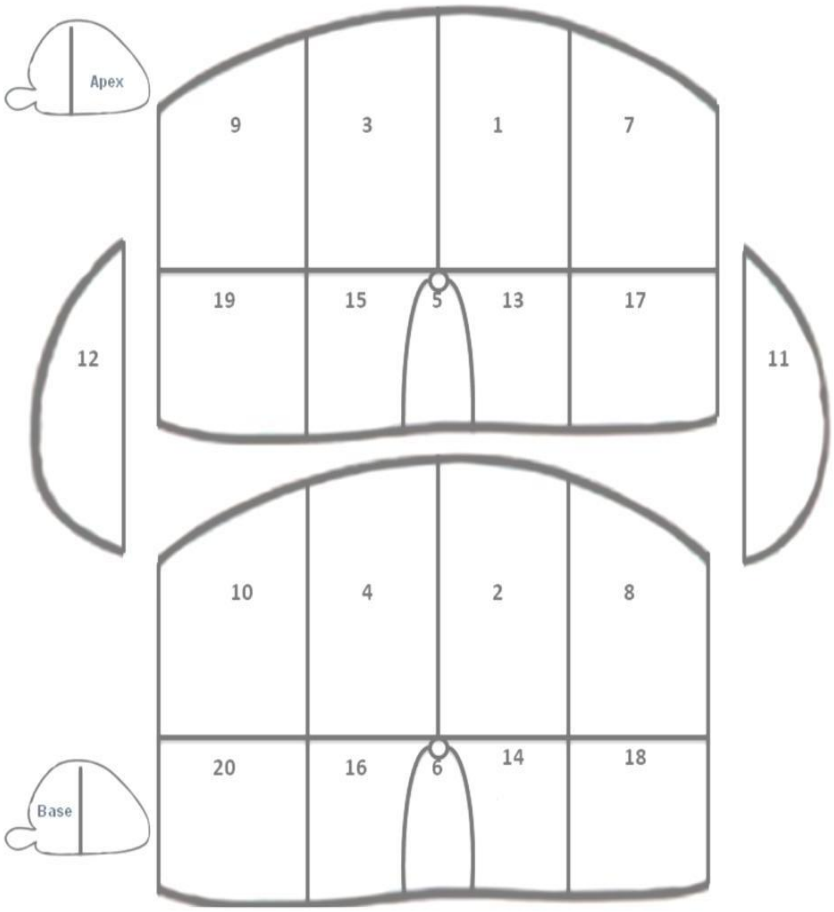


Definition three

Insignificant disease

Our definitions of significance are based on biopsy simulation work carried out at UCLH, using the classic 0.5ml and 0.2ml volume cut offs as described by Dr's Stamey and Epstein[65]. Standardized reports will be constructed for each patient and a histology regional map produced. See Appendix Four - Histopathology Reporting Map.

Barzell Zones



Modified Barzell Zones

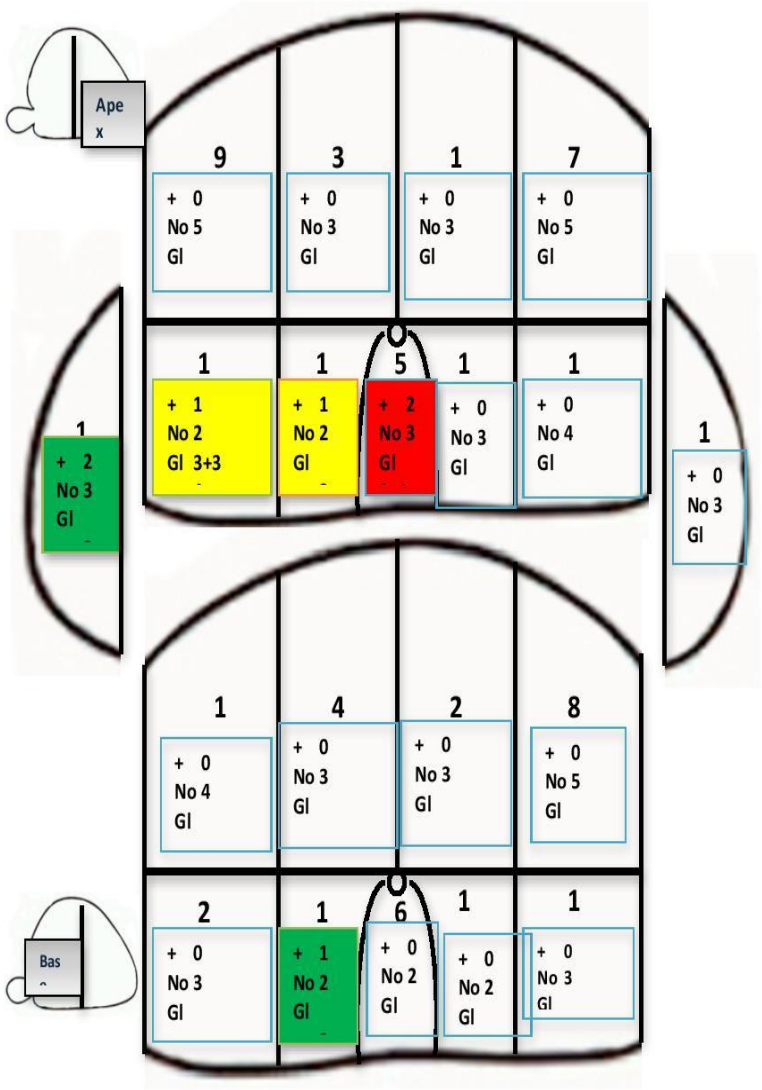
1 Left Parasagital Anterior Apex
2 Left Parasagital Anterior Base
3 Right Parasagital Anterior Apex
4 Right Parasagital Anterior Base
5 Midline Apex
6 Midline Base
7 Left Medial Anterior Apex
8 Left Medial Anterior Base
9 Right Medial Anterior Apex
10 Right Medial Anterior Base
11 Left Lateral
12 Right Lateral
13 Left Parasagital Posterior Apex
14 Left Parasagital Posterior Base
15 Right Parasagital Posterior Apex
16 Right Parasagital Posterior Base
17 Left Medial Posterior Apex
18 Left Medial Posterior Base
19 Right Medial Posterior Apex
20 Right Medial Posterior Base

Histopathology Reporting Map - Example

Name:
Hospital Number:
Date of Birth:
Date:

University College London Hospitals NHS
NHS Foundation Trust

Template Mapping



Modified Barzell Zones

1 Left Parasagital Anterior Apex
2 Left Parasagital Anterior Base
3 Right Parasagital Anterior Apex
4 Right Parasagital Anterior Base
5 Midline Apex
6 Midline Base
7 Left Medial Anterior Apex
8 Left Medial Anterior Base
9 Right Medial Anterior Apex
10 Right Medial Anterior Base
11 Left Lateral
12 Right Lateral
13 Left Parasagital Posterior Apex
14 Left Parasagital Posterior Base
15 Right Parasagital Posterior Apex
16 Right Parasagital Posterior Base
17 Left Medial Posterior Apex
18 Left Medial Posterior Base
19 Right Medial Posterior Apex
20 Right Medial Posterior Base

No cancer

Clinically insignificant disease

Gleason = 3+4 AND/OR
Max Cancer length 4-5mm

Gleason >/= 4+3 AND/OR
Max cancer length >/=6mm

Appendix Five - Focal salvage Treatment

Focal Salvage HIFU

6 weeks after TPM patients will have focal salvage HIFU.

This is a day case procedure performed under general anaesthetic. Unless there are any contra-indications a dose of 120-160mg of intravenous Gentamicin will be given as antibiotic prophylaxis. A suprapubic catheter will be inserted under cystoscopic guidance before the proposed HIFU treatment.

Three-dimensional ultrasound images will be taken to allow registration with MRI both pre-treatment and post-treatment in order to evaluate whether the treatment protocol was effective in ablating the lesion. The HIFU probe and machine will be prepared as per the manufacturer's instructions. Once this is done the probe is introduced into the rectum with as little trauma as possible. Views of the prostate are then obtained to ensure that the images are of high quality and that the proposed therapy is technically feasible.

Post Focal HIFU

Post-treatment the suprapubic catheter will be attached to a catheter bag on free drainage. This will be changed the following day to a flip-flow valve thereby allowing the patient to return to a normal voiding pattern sooner. Catheter care advice will be given to the patient prior to discharge. Analgesia (such as co-dydramol 10/500, paracetamol or diclofenac), antibiotics (quinolones for 1 week) and laxatives will be provided as part of post-operative care.

Suprapubic catheter withdrawal will occur under antibiotic cover in a clinic setting 7 days after treatment at the treating centre or locally by a practice nurse or district nurse. If the patient fails to void, he will be taught CISC. Failure to void requiring hospitalisation is an expected side-effect of HIFU therapy and will not be reported as a serious adverse event that requires reporting to the sponsor or the Ethics Committee.

Cryotherapy

Treatment with Cryotherapy

Signed informed consent will be taken for the focal ablation procedure using cryotherapy. Patients will be admitted on the day of the procedure or the evening before as appropriate. A phosphate enema will be administered on the morning of surgery to ensure an empty rectum. The type of anaesthesia (regional/ general) will be discussed with the patient and depend on the anaesthetic opinion. The type of anaesthesia chosen will aim to eliminate any patient movement during cryotherapy treatment to avoid any adverse complications. The patient will be placed in a relaxed lithotomy position. TED stockings and Flowtron boots will be fitted to the patient's legs for prophylaxis against any potential thrombo-embolic event. In accordance with local hospital policy sub-cutaneous heparin may be administered peri-operatively. Unless there are any contra-indications a dose of 120-160mg of intravenous Gentamicin will be given as antibiotic prophylaxis. A suprapubic catheter will be inserted under cystoscopic guidance before the proposed cryotherapy treatment.

A warming catheter is used to protect the urethra from freezing since the urethra passes through the prostate gland. An ultrasound probe in the rectum is then used to guide cryotherapy needles via the perineum into the prostate. MTS™ (Multi-point Thermal Sensor) and thermal sensor needles keep monitor of the temperature within and around

the prostate to ensure that the prostate is being frozen to temperatures less than -40^0. Celsius while the adjacent areas of the rectum and other organs are not frozen. The use of the MTS needles to monitor temperatures of the entire prostate and surrounding tissues dramatically lowers the chance of incontinence, rectal fistulae or other side effects.

When the cryoablation needles and temperature sensors are in place, a freezing agent, Argon gas, is circulated through the cryoablation needles to create temperatures of minus 40 degree Celsius or colder. Circulating the extremely cold argon gas through the cryoablation needles creates a lethally cold iceball that freezes the prostate and the cancer cells in it. Once the targeted area is frozen, the thawing is employed. The thawing process ruptures and kills the cells in the prostate gland. This is called the freeze-thaw process. This process is repeated to ensure all cancerous cells are destroyed. Throughout the cryoablation procedure, temperature sensors are used to determine when target temperatures have been reached. The cancer tumor and its blood supply are destroyed and the dead tissue is re-absorbed or remains in the body as harmless scar tissue.

When the freeze-thaw process is finished, the warming catheter is removed and a urinary catheter is inserted in place to help with any temporary urinary incontinence.

Known and Potential Risks of Whole-gland Salvage Cryotherapy

Swelling of the penis or scrotum may occur. The gland swells, preventing urine from leaving the bladder. If this happen the catheter may have to remain for a few weeks until the swelling subsides. The perineum (the area between the anus and scrotum) may also swell/be uncomfortable/painful. Simple analgesia/application of ice packs will be advised. Scrotal oedema may also occur.

Freezing may affect the bladder and intestines, which can lead to pain, dysuria and frequency. Most men recover normal bladder function in a matter of weeks. Doctors may also prescribe some medication for bladder spasms. Many men will also experience blood in the urine.

Suprapubic catheter withdrawal will occur under antibiotic cover in a clinic setting 7 days after treatment at the treating centre or locally by a practice nurse or district nurse. If the patient fails to void, he will be taught CISC. Failure to void requiring hospitalisation is an expected side-effect of cryotherapy and will not be reported as a serious adverse event that requires reporting to the sponsor or the Ethics Committee.

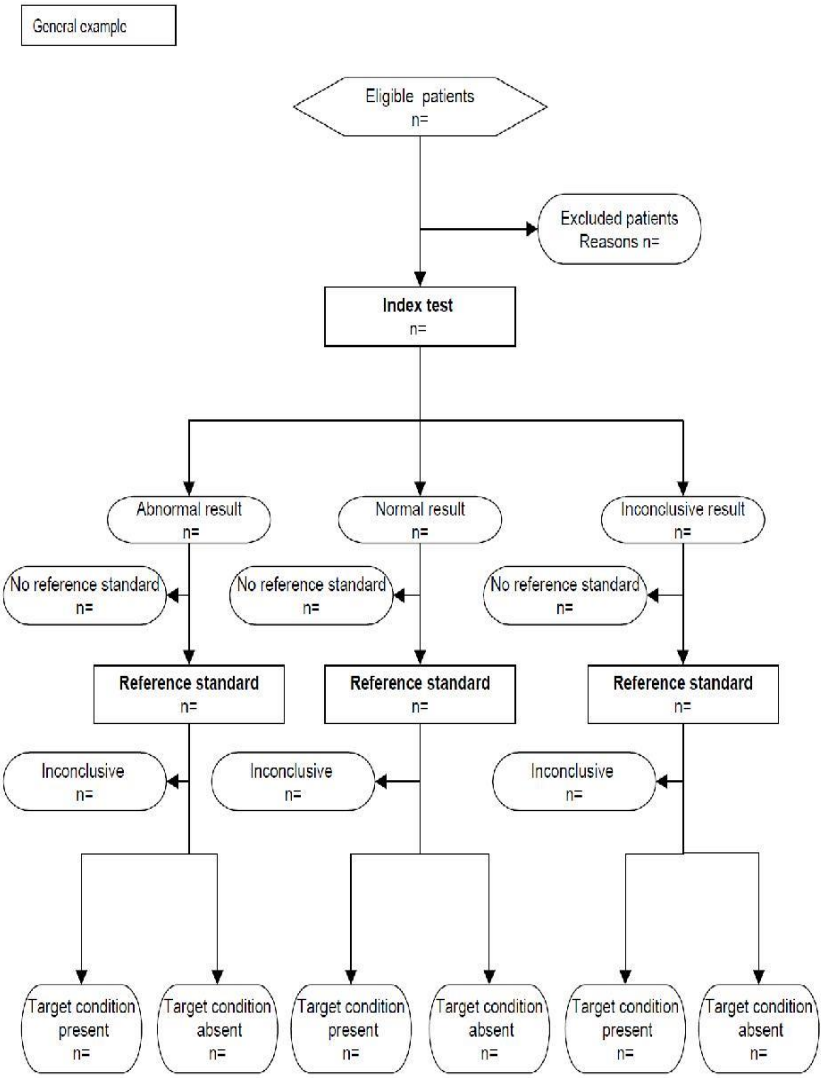
Appendix Six - Analysis plan

A full and detailed statistical analysis plan will be produced prior to the commencement of the final analysis; a summary of the intended plan is provided here.

6.1 Baseline Demographics

Baseline Characteristics
Age (years), mean (SD, range)
Serum PSA (ng/ml), mean (SD, range)
Prostate Volume at MRI (ml), mean (SD, range)
PSA Density (ng/ml/ml), mean (SD, range) for MRI
Previous Hormone treatment, % (N)
Transperineal template prostate mapping biopsy characteristics
Transperineal Template Prostate Mapping Biopsy, mean (SD, range) Total Cores Total Positive Cores % Positive Cores Core density (biopsies/ml)
Gleason at Transperineal Template Prostate Mapping Biopsy Negative 3+3 3+4 4+3 4+4 4+5 5+4 5+5
Maximum cancer core length (mm) Number of patients at each core length from 1mm – 12mm
Location of disease at transperineal template prostate mapping biopsy, % (N) No disease Unilateral Bilateral Further breakdown per modified Barzell zone
Risk category after transperineal template prostate mapping biopsy, % (N) Benign Low Intermediate High

Results from this study will be reported according the Standard of Reporting Diagnostic Accuracy (STARD) guidelines.


General example
Eligible patients
n=
Excluded patients
Reasons n=
Index test
n=
Abnormal result
n=
Normal result
n=
Inconclusive result
n=
No reference standard
n=
No reference standard
n=
No reference standard
n=
Reference standard
n=
Reference standard
n=
Reference standard
n=
Inconclusive
n=
Inconclusive
n=
Inconclusive
n=
Target condition present
n=
Target condition absent
n=
Target condition present
n=
Target condition absent
n=
Target condition present
n=
Target condition absent
n=

6.2 Analysis of Multi-parametric MRI and Prostate Mapping biopsy results

Results will be presented in a 2 by 2 tables (as shown below) and estimates will be presented together with 95% confidence intervals (CI).
2 by 2 tables to demonstrate accuracy of mpMRI with respect to TPM

		MRI score		
		+ve	- ve	Total
TPM	+ve	a	b	a+b
	- ve	c	d	c+d

Sensitivity = a / (a+b) where, a = number of men testing positive on MRI and positive for clinically significant on TPM, b = number of men testing negative for MRI who have clinically significant cancer on TPM.
Specificity = d / (c+d) where, d = number of men testing negative on MRI and negative for clinically significant cancer on TPM, c = number of men testing positive on MRI who have clinically insignificant cancer on TPM.
Negative Predictive Value (NPV) = d / (b+d) where, d = number of men testing negative on MRI and negative for clinically significant cancer on TPM, b= number of men testing negative on MRI who have clinically significant cancer on TPM.
Positive Predictive Value (PPV) = a / (a+c) where, a = number of men testing positive on MRI and positive for clinically significant on TPM, c = number of men testing positive on MRI who have clinically insignificant cancer on TPM.
Varying the positive cut off for MRI
The above analysis will be performed using MRI scores:

- ≥3 as positive
- ≥4 as positive
- ≥5 as positive
-

MRI to TPM 2 by 2 tables will be constructed for both High risk and intermediate risk according to the criteria below, which is an adaptation of our definitions of clinical significance that include the total cancer core length of positive biopsy cores within a modified Barzell zone. (UCL definition 2)

6.3 Varying the definitions of clinical significance at TPM

2 by 2 tables will be constructed for MRI comparison to TPM at patient level for:

- Definition 1 disease
- Definition 2 disease
- All cancer
- For a combination of thresholds for significance at TPM selected from the below table:
  (NB Red highlighted= Definition 1, Yellow=Definition 2, Green= Insignificant disease)

Gleason 4+3 AND/OR MCCL ≥ 10mm	Gleason 3+4 AND/OR MCCL ≥ 10mm	Gleason 3+3 AND/OR MCCL ≥ 10mm
Gleason 4+3 AND/OR MCCL ≥ 9mm	Gleason 3+4 AND/OR MCCL ≥ 9mm	Gleason 3+3 AND/OR MCCL ≥ 9mm
Gleason 4+3 AND/OR MCCL ≥ 8mm	Gleason 3+4 AND/OR MCCL ≥ 8mm	Gleason 3+3 AND/OR MCCL ≥ 8mm
Gleason 4+3 AND/OR MCCL ≥ 7mm	Gleason 3+4 AND/OR MCCL ≥ 7mm	Gleason 3+3 AND/OR MCCL ≥ 7mm
Gleason 4+3 AND/OR MCCL ≥ 6mm	Gleason 3+4 AND/OR MCCL ≥ 6mm	Gleason 3+3 AND/OR MCCL ≥ 6mm
Gleason 4+3 AND/OR MCCL ≥ 5mm	Gleason 3+4 AND/OR MCCL ≥ 5mm	Gleason 3+3 AND/OR MCCL ≥ 5mm
Gleason 4+3 AND/OR MCCL ≥ 4mm	Gleason 3+4 AND/OR MCCL ≥ 4mm	Gleason 3+3 AND/OR MCCL ≥ 4mm
Gleason 4+3 AND/OR MCCL ≥ 3mm	Gleason 3+4 AND/OR MCCL ≥ 3mm	Gleason 3+3 AND/OR MCCL ≥ 3mm
Gleason 4+3 AND/OR MCCL ≥ 2mm	Gleason 3+4 AND/OR MCCL ≥ 2mm	Gleason 3+3 AND/OR MCCL ≥ 2mm
Gleason 4+3 AND/OR MCCL ≥ 1mm	Gleason 3+4 AND/OR MCCL ≥ 1mm	Gleason 3+3 AND/OR MCCL ≥ 1mm

This will allow us to show at which cut off values for disease significance MRI performs best.

Summarizing results

The performance characteristics for mp-MRI will be summarized using receiver operator curves (ROC) and measures of the area under the curve.

6.4 Analysis of Targeted sampling

Transperineal Template prostate Mapping biopsy and Targeted biopsy characteristics
Transperineal Template Prostate Mapping Biopsy, mean (SD, range) and per patient analysis. Total Cores- Number of standard cores Number of targeted cores Total Positive Cores – Standard cores positive, % (N) Targeted cores Positive, % (N) Cognitive MRI Targeted cores Positive, % (N) MRI/US registration Targeted cores Positive, % (N)
Gleason scores at Transperineal Template Prostate Mapping Biopsy in targeted cores: Distribution of Gleason scores for: All Targeted cores Cognitive MRI Targeted cores MRI/US registration Targeted cores
Location of disease at transperineal template prostate mapping biopsy using targeted cores only, % (N) No disease Unilateral Bilateral Further breakdown per modified Barzell zone
Risk category using targeted biopsy cores (%, n) For All Targeted cores Cognitive MRI Targeted cores MRI/US registration Targeted cores

We will examine how representative of cancer burden the targeted cores are, in comparison to the standard template biopsy cores.
We will also assess the number of patients exclusively positive on targeted sampling.
The following tables will be used:

N= number of pts		**Template Biopsy**		
		Clinically Significant	Clinically Insignificant	No cancer
	Clinically Significant			
Cognitive MRI Targeted Biopsy	Clinically Insignificant			
	No cancer			

		Template Biopsy		
		Clinically Significant	Clinically Insignificant	No cancer
	Clinically Significant			
MRI/US registration Targeted Biopsy	Clinically Insignificant			
	No cancer			

6.5 Matching between Index tests and reference test

Paired analysis at various levels for both Index tests

Paired analysis between WB-MRI, Choline-PET and TPM will be performed for the objective at the patient level (whole gland). This will allow us to see how useful each of the tests might be as a triage tool for biopsy.

For the purpose of further paired analysis, each prostate is further divided into different regions of interest and the assumption is made that each region is independent of the other.

The analyses steps used for MRI-TB vs WBMRI will be repeated for:

- Hemi Gland analysis (Left/Right)
- Quadrant (Left/Right, Anterior/Posterior)
- 12 regions of interest

We are repeating our analysis with a number of different regions of interest to assess whether negative areas on the imaging modalities can be safely excluded from further biopsy.

Also to allow us to assess how the methodology of analysis by prostate division differs the results of the tests validity.

Prostate division will utilise the urethra as midline for division of laterality between left and right.

The division of anterior to posterior will be set 1.7cm from the posterior border of the prostate capsule in the midline. The rationale for this is that the average TRUS biopsy throw is 1.7cm and thus we will be able to identify those men in whom TRUS biopsy was likely to never identify lesions.

The 12 regions of interest are the above quadrantic divisions further subdivided into apex, midgland and basal regions.

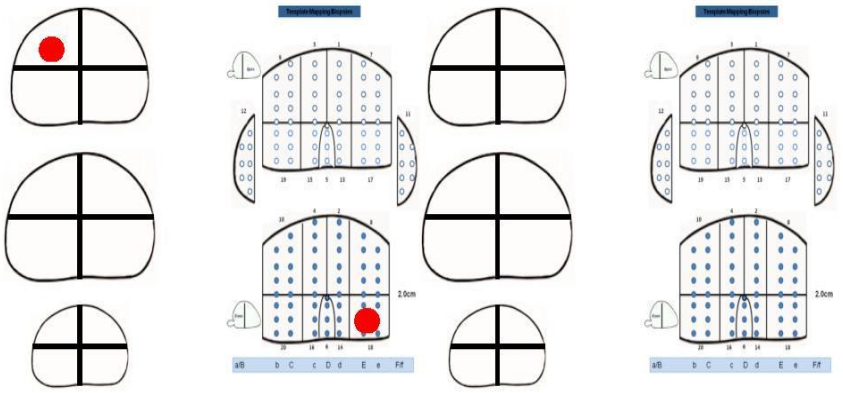
The transperineal template prostate mapping biopsy is taken in 20 modified Barzell zones, not the above divisions, therefore strict criteria for matching between the Index tests and the reference test will need to be decided upon.

For all lesions on the index test crossing a boundary marker they will only count as POSITIVE for the region in which they are most dominant. However this may reflect as a reduction in sensitivity.

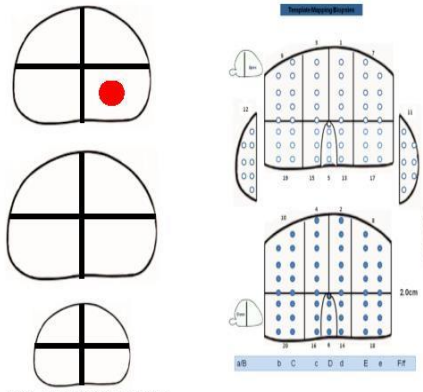
Whole gland

For the whole gland analysis matching is more straightforward, if cancer is found on the index test and cancer satisfying the criteria for significance in the reference test is found this will be a TRUE POSITIVE- irrespective of location of cancer foci. The absence of cancer in both the index and reference test will equal a TRUE NEGATIVE.

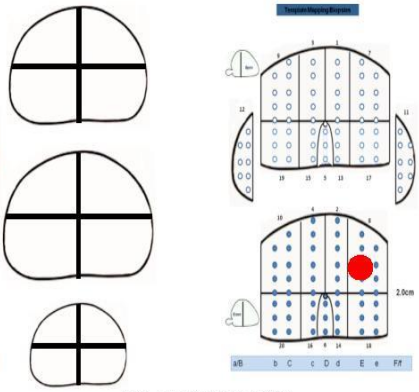
Cancer found in the Index test but not in the reference will be a FALSE POSITIVE. Cancer not found at the index test but present on the reference will be a FALSE NEGATIVE. The diagrams below represent whole gland matching:



TRUE POSITIVE



TRUE NEGATIVE



FALSE POSITIVE

FALSE NEGATIVE

Hemi Gland

The transperineal template prostate mapping biopsy Barzell zones 5 and 6 lie in the midline, which creates a boundary issue.

This will be dealt with by using the rule that if cancer is present in either of the midline zones, 5+6, it will be deemed as present on both hemi glands (i.e. Left and Right), and the Index tests will be rated accordingly.

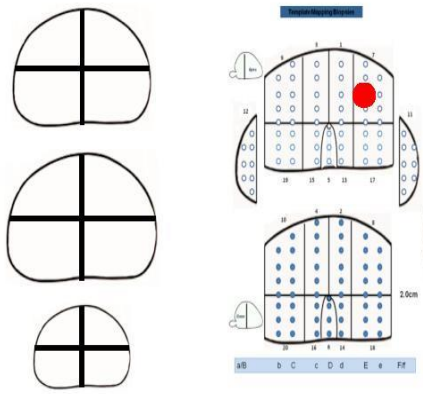
If both zones 5 and 6 do not contain cancer, they will be deemed negative for the purpose of analysis.

TRUE POSITIVE= Cancer in the index test and also the reference test within the same laterality.

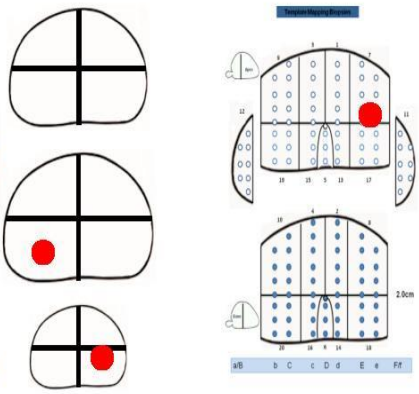
TRUE NEGATIVE= No cancer in either the index or reference test in the same laterality.

FALSE POSITIVE= Cancer in the index test hemi gland, not found in the reference test.

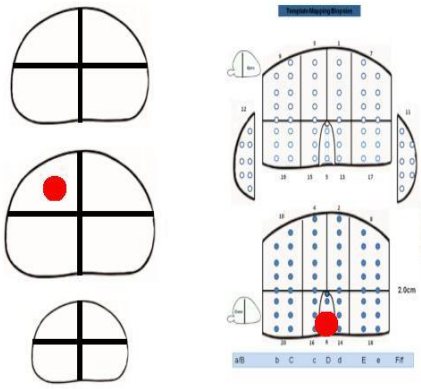
FALSE NEGATIVE= Cancer not found in the index test hemi gland that is present in the reference test.



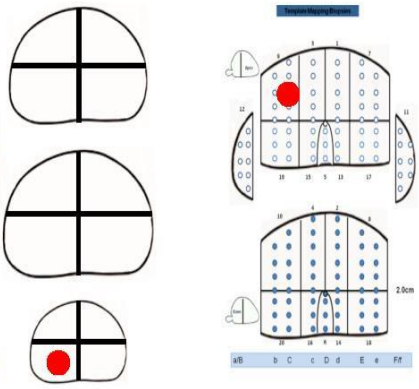
TRUE NEGATIVE on RIGHT
FALSE NEGATIVE on LEFT



FALSE POSITIVE on RIGHT
TRUE POSITIVE on LEFT



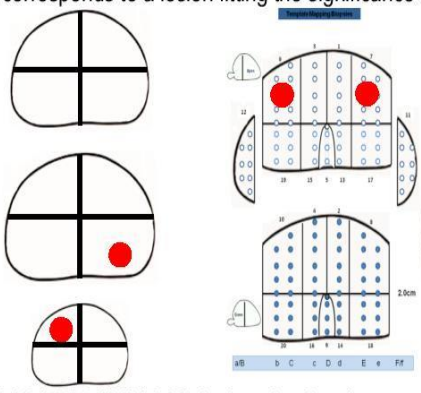
TRUE POSITIVE- on RIGHT
FALSE NEGATIVE on LEFT



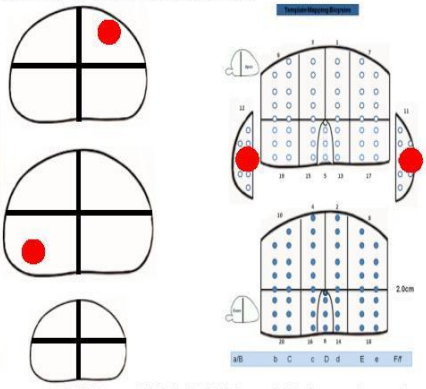
TRUE POSITIVE on RIGHT
TRUE NEGATIVE on LEFT

Quadrant analysis

The rule for midline zones that applies to Hemi-gland analysis will remain in place for the quadrantic analysis.
Further subdivision into anterior and posterior regions will enforce a similar rule to be decided upon for the lateral Barzell segments, **11+12**, as these are not routinely divided into anterior and posterior.
Because of deformation at the time of transperinal template prostate mapping biopsies by the ultrasound probe, zones 11 and 12 are most likely to represent mainly posterior tissue, they will therefore be analysed as part of the **posterior quadrants**.
The Z axis location the lesion- i.e. Apex, Midgland, Base, has no bearing on matching, as long as a lesion is called in the correct laterality and Y axis i.e. Anterior/Posterior, that corresponds to a lesion fitting the significance criteria in the reference test.



TRUE POSITIVE- Right Anterior Quadrant
TRUE NEGATIVE- Right Posterior Quadrant
FALSE NEGATIVE –Left Anterior Quadrant
FALSE POSITIVE- Left Posterior Quadrant



TRUE NEGATIVE- Right Anterior Quadrant
TRUE POSITIVE- Right Posterior Quadrant
FALSE POSITIVE- Left Anterior Quadrant
FALSE NEGATIVE- Left Posterior Quadrant

12 Regions of Interest

The previous rules regarding region of interest boundaries will still apply to the 12 RoI divisions, for laterality and anterior/posterior divisions.
However the Z axis, depth of a lesion will now be applied
The Index tests will be divided into Apex, Midgland and Base.

Transperineal template prostate mapping biopsy cores are taken only in two levels, and as we are not designating orientation of the biopsy cores we will not be able to divide biopsies into these same thirds.

Lesions identified by the index tests in the Apices will be deemed positive if the corresponding cores from odd numbered Barzell zones are positive, according to the already set out rules regarding laterality and anterior/posterior divisions. Zones 1, 3, 5, 7, 9, 11, 13, 15, 17, and 19 are apical.

As the midgland does not have its own biopsy throw performed lesions called by the index test within the midgland will be deemed positive if found in the apical TPM cores as the apical throw also covers the midgland level.

Lesions identified by the index tests in the Base will be deemed positive if the corresponding cores from the even numbered Barzell zones are positive according to the already set out rules regarding laterality and anterior/posterior divisions. Zones 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 are basal.

6.7 Focal Salvage HIFU/Cryotherapy Analysis

The following tables will be constructed:
Descriptive tables as shown below will be populated

Baseline Characteristics
Age (years), mean (SD, range)
Serum PSA (ng/ml), mean (SD, range)
Prostate Volume (ml), mean (SD, range)
Gleason (TTPM) 3+3 3+4 4+3
TTPM, mean (SD, range) Total Cores Total Positive Cores % Positive Cores Core density (biopsies/ml)
Risk category after TTPM (%, n) Low Intermediate

Peri-operative Characteristics
Procedure time (SPC and Hemi-HIFU) (minutes), mean (SD, range)
Discharge time from procedure end (hours), mean (SD, range)
Length of suprapubic catheterisation (days), mean (SD, range)[#]
Dysuria (negative urine culture), % (n) Duration (days), mean (SD, range)
Intermittent haematuria (start of stream only), % (n) Duration (days), mean (SD, range)
Urinary debris, % (n) Duration (days), mean (SD, range)
Urinary tract infection (positive urine culture) (%, n)
Stricture (%, n)
Recto-urethral fistula (%, n)

Post-operative Characteristics
PSA (ng/ml), mean (SD, range)
1 mth
3 mth
6 mths
MRI score at 12 months

Reference List

[1] Roach M 3rd, Hanks G, Thames H Jr et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys. 2006 Jul 15;65(4):965-74.

[2] Critz FA, Williams WH, Benton JB, Levinson AK, Holladay CT, Holladay DA. Prostate specific antigen bounce after radioactive seed implantation followed by external beam radiation for prostate cancer. *J Urol* 2000; 163: 1085–9

[3] Rosser CJ, Kuban DA, Levy LB *et al*. Prostate specific antigen bounce phenomenon after external beam radiation for clinically localized prostate cancer. *J Urol* 2002; 168: 2001–5

[4] Hanks GE, Hanlon AL, Schultheiss TE *et al*. Conformal external beam treatment of prostate cancer. *Urology* 1997; 50: 87– 92

[5] Cavanagh W, Blasko JC, Grimm PD et al. Transient elevation of serum prostate-specific antigen following 125I/103Pd brachytherapy for localized prostate cancer. *Semin Urol Oncol* 2000; 18: 160–5

[6] Taylor LG, et al. Review of major adverse effects of androgen-deprivation therapy in men with prostate cancer. Cancer. 2009;115(11):2388-99

[7] Tannock IF, De Wit R, Berry WR e tal. TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004;351:1502---12.

[8] Ryan C, Efstathiou E, Smith M et al. Phase II multicenter study of chemotherapy (chemo)-naive castration-resistant prostate cancer (CRPC) not exposed to ketoconazole (keto), treated with abiraterone acetate (AA) plus prednisone. J Clin Oncol. 2009;27:15s [Abstract 5046].

[9] De Bono JS, Logothetis CJ, Molina A et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 364(21):1995-2005. Epub 2011/05/27

[10] Higano CS, Schellhammer PF, Small EJ et al. Integrated data from 2 randomized, double-blind, placebocontrolled, phase 3 trials of active cellular immunotherapy with sipuleucel-T in advanced prostate cancer. Cancer. 2009;115(16):3670-9. Epub 2009/06/19, http://dx.doi.org/10.1002/cncr.24429.

[11] Scher H, Fizazi K, Saad F et al. Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy N Engl J Med 2012; 367:1187-1197September 27, 2012

[12] Nilsson S, Franzén L, Parker C. Bone-targeted radium-223 in symptomatic, hormone refractory prostate cancer: a randomised, multicentre, placebo-controlled phase II study. Lancet Oncol 2007; 8: 587–94

[13] Chade DC, Eastham J, Graefen M. Cancer Control and Functional Outcomes of Salvage Radical Prostatectomy for Radiation-recurrent Prostate Cancer: A Systematic Review of the Literature European Urology 61 (2012) 961-971

[14] Ahmed HU, Akin O, Coleman JA et al. Transatlantic Consensus Group on Active Surveillance and Focal Therapy for Prostate Cancer (appendix). Transatlantic Consensus

Group on active surveillance and focal therapy for prostate cancer. BJU Int. 2012 Jun;109(11):1636-47. doi: 10.1111/j.1464-410X.2011.10633.x. Epub 2011 Nov 11. PubMed PMID: 22077593.

[15] Craig P, Dieppe P, Macintyre S. Developing and evaluating complex interventions: new guidance 29 Sep 2008. www.mrc.ac.uk/complexinterventionsguidance

[16] Clamp A, Danson S, Nguyen H et al. Assessment of therapeutic response in patients with metastatic bone disease.(2004) Lancet Oncol 5: 607–616

[17] Taoka T, Mayr NA, Lee HJ et al. Factors influencing visualisation of vertebral metastases on MR imaging versus bone scintigraphy. Am J Roentgenol (2001) 176: 1525– 1530

[18] Bubendorf L, Schopfer A, Wagner U et al. Metastatic patterns of prostate cancer: an autopsy study of 1589 patients. (2000) Hum Path 31: 578–583

[19] Townsend DW. Dual-modality imaging: combining anatomy and function. J Nucl Med 2008;49:938–55

[20] Picchio M, Briganti A, Fanti S et al. The Role of Choline Positron Emission Tomography/Computed Tomography in the Management of Patients with Prostate-Specific Antigen Progression After Radical Treatment of Prostate Cancer. European Urology 59(2011) 51-60

[21] Krause BJ, Souvatzoglou M, Tuncel M, et al. The detection rate of [11C]choline-PET/CT depends on the serum PSA-value in patients with biochemical recurrence of prostate cancer. Eur J Nucl MedMol Imaging 2008;35:18–23.

[22] Richter JA, Rodriguez M, Rioja J, et al. Dual tracer (11)C-choline and FDG-PET in the diagnosis of biochemical prostate cancer relapse after radical treatment. Mol Imaging Biol 2010;12:210–7

[23] Muller SA, Holzapfel K, Seidl C et al. Senekowitsch- Schmidtke R. Characterization of choline uptake in prostate cancer cells following bicalutamide and docetaxel treatment. Eur J Nucl Med Mol Imaging 2009;36:1434–42

[24] Breeuwsma AJ, Pruim J, van den Bergh AC, et al. Detection of local, regional, and distant recurrence in patients with PSA relapse after external-beam radiotherapy using (11)C-choline positron emission tomography. Int J Radiat Oncol Biol Phys 2010;77:160–4.

[25] Giovacchini G, Picchio M, Coradeschi E, et al. [(11)C]choline uptake with PET/CT for the initial diagnosis of prostate cancer: relation to PSA levels, tumour stage and anti-androgenic therapy. Eur J Nucl Med Mol Imaging 2008;35:1065–73

[26] Koh DM, Takahara T, Imai Y, Collins DJ. Practical aspects of assessing tumors using clinical diffusion-weighted imaging in the body. Magn Reson Med Sci 2007;6:211–24.

[27] Komori T, Narabayashi I, Matsumura K, et al. 2-[Fluorine-18]-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography versus whole-body diffusion-weighted MRI for detection of malignant lesions: initial experience. Ann Nucl Med 2007;21: 209–15.

[28] Heliou R, Normandeau L, Beaudoin G. Towards dose reduction in CT: patient radiation dose assessment for CT examinations at University Health Center in Canada and comparison with national diagnostic reference levels. Radiat Prot Dosimetry 2012;148: 202–10.

[29] Lecouvet FE, El Mouedden J, Collette L et al. Can whole-body magnetic resonance imaging with diffusion-weighted imaging replace Tc 99m bone scanning and computed tomography for single-step detection of metastases in patients with high-risk prostate cancer? Eur Urol. 2012 Jul;62(1):68-75.

[30] Venkitaraman R , Cook GJR, Dearnaley DP, et al. Whole-body magnetic resonance imaging in the detection of skeletal metastases in patients with prostate cancer *Journal of Medical Imaging and Radiation Oncology* 53 (2009) 241–247

[31] Jacobs MA, Ouwerkerk R, Petrowski K et al. Diffusion-weighted imaging with apparent diffusion coefficient mapping and spectroscopy in prostate cancer. Top Magn Reson Imaging 2008;19:261–72

[32] Mazaheri Y, Shukla-Dave A, Muellner A et al. MR imaging of the prostate in clinical practice. MAGMA 2008;21:379–92

[33] Sciarra A, Panebianco V, Salciccia S, et al. Modern role of magnetic resonance and spectroscopy in the imaging of prostate cancer. Urol Oncol 2011;1:12–20.

[34] Somford DM, Futterer JJ, Hambrock T et al. Diffusion and perfusion MR imaging of the prostate. Magn Reson Imaging Clin N Am 2008;16:685–95.

[35] Seitz M, Shukla-Dave A, Bjartell A, et al. Functional magnetic resonance imaging in prostate cancer. Eur Urol 2009;55:801–14.

[36] Kara T, Akata D, Akyol F et al. The values of dynamic contrast-enhanced MRI in the detection of recurrent prostate cancer after external beam radiotherapy: correlation with transrectal ultrasound and pathological findings. Diagn Interv Radiol. In press. DOI:10.4261/1305-3825.

[37] Haider MA, Chung P, Sweet J et al. Dynamic contrast-enhanced magnetic resonance imaging for localization of recurrent prostate cancer after external beam radiotherapy. Int J Radiat Oncol Biol Phys. 2008 Feb 1;70(2):425-30. Epub 2007 Sep 19. PubMed PMID: 17881141.

[38] Arumainayagam N, Kumaar S, Ahmed HU et al. Accuracy of multiparametric magnetic resonance imaging in detecting recurrent prostate cancer after radiotherapy. British Journal of Urology International. 2010; 106,991-997

[39] Kanthabalan A, Abl-Azzeez M, Arya M et al. Transperineal MRI-targeted biopsy versus transperineal template prostate mapping biopsy in the detection of localised radio-recurrent prostate cancer. Abstract accepted EAU 2013

[40] Dudderidge T, Payne H, Emberton M. An algorithm for managing the failure of external beam radiotherapy in prostate cancer. BJU Int. 2007 Sep;100(3):518-27.

[41] Merrick GS, Gutman S, Andreini H et al. Prostate cancer distribution in patients diagnosed by transperineal template-guided saturation biopsy. Eur Urol 2007 Sep;52(3):715-23.

[42] Crook J, Malone S, Perry G et al. Postradiotherapy prostate biopsies: what do they really mean? Results for 498 patients. *Int J Radiat Oncol Biol Phys* 2000; 48: 355–67

[43] Bostwick DG, Egbert BM, Fajardo LF. Radiation injury of the normal and neoplastic prostate. *Am J Surg Pathol* 1982; 6: 541–51

[44] Miller EB, Ladaga LE, el-Mahdi AM et al. Reevaluation of prostate biopsy after definitive radiation therapy. *Urology*. Apr 1993;41(4):311-6

[45] Crawford ED, Wilson SS, Torkko KC et al. Clinical staging of prostate cancer: a computer-simulated study of transperineal prostate biopsy. BJU Int 2005 Nov;96(7):999-1004

[46] Merrick GS, Gutman S, Andreini H et al. Prostate cancer distribution in patients diagnosed by transperineal template-guided saturation biopsy. Eur Urol 2007 Sep;52(3):715-23.

[47] Hu Y, Ahmed HU, Taylor Z et al. MR to ultrasound registration for image-guided prostate interventions. Med Image Anal 2010 Dec 13.
.

[48] Murat FJ, Poissonnier L, Rabilloud M *et al.* Mid-term results demonstrate salvage high-intensity focused ultrasound (HIFU) as an effective and acceptably morbid salvage treatment option for locally radiorecurrent prostate cancer. *Eur Urol* 2008; 55: 640–9

[49] Uddin Ahmed H, Cathcart P, Chalasani V, Whole-gland salvage high-intensity focused ultrasound therapy for localized prostate cancer recurrence after external beam radiation therapy. Cancer. 2012 Jun 15;118(12):3071-8.

[50] Chalasani V, Martinez CH, Lim D, Chin J. Salvage HIFU for recurrent prostate cancer after radiotherapy. *Prostate Cancer Prostatic Dis* 2009; 12: 124–9

[51] Rebillard X, Soulie M, Chartier-Kastler E *et al.* High-intensity focused ultrasound in prostate cancer; a systematic literature review of the French Association of Urology. *BJU Int* 2008; 101: 1205–13

[52] Gelet A, Chapelon JY, Poissonnier L *et al.* Local recurrence of prostate cancer after external beam radiotherapy: early experience of salvage therapy using high intensity focused ultrasonography. *Urology* 2004; 63: 625–9

[53] Ahmed HU, Cathcart P, McCartan N et al. Focal salvage therapy for localized prostate cancer recurrence after external beam radiotherapy: a pilot study. Cancer. 2012 Sep 1;118(17):4148-55.

[54] Gage AA, Baust J (1998) Mechanisms of tissue injury in cryosurgery. Cryobiology 37(3): 171–186.

[55] Hoffmann NE, Bischof JC (2002) The cryobiology of cryosurgical injury. Urology 60(2 suppl. 1): 40– 49.

[56] Baust JG et al (2009) The pathophysiology of thermoablation: optimizing cryoablation. Curr Opin Urol 19(2): 127–132.

[57] Ismail M, Ahmed S, Kastner C et al. Salvage cryotherapy for recurrent prostate cancer after radiation failure: a prospective case series of the first 100 patients. *BJU Int* 2007; 100: 760–4

[58] Pisters LL, Rewcastle JC, Donnelly BJ et al. Salvage prostate cryoablation: initial results from the cryo on-line data registry. *J Urol* 2008; 180: 559–63

[59] Ahmed S, Lindsey B, Davies J. Salvage cryosurgery for locally recurrent prostate cancer following radiotherapy. *Prostate Cancer Prostatic Dis* 2005; 8: 31–5

[60] Galosi AB, Lugnani F, Muzzonigro G. Salvage cryosurgery for recurrent prostate carcinoma after radiotherapy. *J Endourol* 2007; 21: 1–7

[61] Ng CK, Moussa M, Downey DB et al. Salvage cryoablation of the prostate: Follow up and analysis of predictive factors for outcome. *J Urol* 2007; 178:1253–7

[62] Nguyen P, D'amico AV, Lee AK, et al. Patient selection, cancer control, and complications after salvage local therapy for postradiation prostate-specific antigen failure. Cancer 2007;110:1417–28.

[63] Mouraviev V, Spiess PE, Jones JS. Salvage cryoablation for locally recurrent prostate cancer following primary radiotherapy. Eur Urol. 2012 Jun;61(6):1204-11. doi: 10.1016/j.eururo.2012.02.051. Epub 2012 Mar 8. Review. PubMed PMID: 22421081.

[64] Eisenberg ML, Shinohara K. Partial salvage cryoablation of the prostate for recurrent prostate cancer after radiotherapy failure. Urology. 2008;72:1315-1318.

[65] Ahmed HU, Hu Y, Carter T et al. Characterizing Clinically Significant Prostate Cancer Using Template Prostate Mapping Biopsy. J Urol 2011 Jun 14.

10.2 Quality of life Questionnaires

Patient Questionnaire – Post Treatment……Months

Please add the date in which you fill the questionnaires here:

Patient Identity:

Please answer all parts of the following trial questionnaires. The phrasing used is from the official questionnaires, which we are unable to alter. However, please adapt each question as appropriate to your own sexual orientation and status.

A. International Prostate Symptom Score (IPSS)

Please Circle Answers

How often over the past month,	Not at all	Rarely	Less than half	About half	More than half	Almost always
Have you felt that you did not empty your bladder completely?	0	1	2	3	4	5
Have you had to pass water more than once in two hours?	0	1	2	3	4	5
Has the flow stopped and started?	0	1	2	3	4	5

Did you have to rush quickly to get to the toilet?	0	1	2	3	4	5
Was the force of the stream reduced?	0	1	2	3	4	5
Did you have difficulty starting to pass water?	0	1	2	3	4	5

How many times do you typically get up at night to urinate?	0	1	2	3	4	5 or more

Total IPSS Score (Maximum: 35)……..

IPSS-Quality of Life

How would you feel if you had to spend the rest of your life with your waterworks the same as they are now?

Delighted	Pleased	Mostly satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
0	1	2	3	4	5	6

B. 15-Item International Index of Erectile Function (IIEF-15)

Please answer the following questions as honestly and clearly as possible.
In answering these questions, the following definitions apply:

- Sexual activity includes intercourse, caressing, foreplay and masturbation
- Sexual intercourse is defined as vaginal penetration of the partner (you entered your partner)
- Sexual stimulation includes situations like foreplay with a partner, looking at erotic pictures, etc.

- Ejaculate is the ejection of semen from the penis (or the feeling of this)

Please Circle One Number

1. Over the past 4 weeks how often were you able to get an erection during sexual activity?

No sexual activity	0
Almost never/never	1
A few times (much less than half the time)	2
Sometimes (about half the time)	3
Most times (much more than half the time)	4
Almost always/always	5

2. Over the past 4 weeks when you had erections with sexual stimulation, how often were your erections hard enough for penetration?

No sexual activity	0
Almost never/never	1
A few times (much less than half the time)	2
Sometimes (about half the time)	3
Most times (much more than half the time)	4
Almost always/always	5

3. Over the past 4 weeks when you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?

Did not attempt intercourse	0
Almost never/never	1
A few times (much less than half the time)	2
Sometimes (about half the time)	3
Most times (much more than half the time)	4
Almost always/always	5

4. Over the past 4 weeks during sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?

Did not attempt intercourse	0
Almost never/never	1

A few times (much less than half the time)	2
Sometimes (about half the time)	3
Most times (much more than half the time)	4
Almost always/always	5

5. Over the past 4 weeks during sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?

Did not attempt intercourse	1
Very difficult	2
Difficult	3
Slightly difficult	4
Not difficult	5

6. Over the past 4 weeks how many times have you attempted sexual intercourse?

No attempts	0
One to two attempts	1
Three to four attempts	2
Five to six attempts	3
Seven to ten attempts	4
Eleven + attempts	5

7. Over the past 4 weeks when you attempted sexual intercourse, how often was it satisfactory for you?

Did not attempt intercourse	0
Almost never/never	1
A few times (much less than half the time)	2
Sometimes (about half the time)	3
Most times (much more than half the time)	4
Almost always/always	5

8. Over the past 4 weeks how much have you enjoyed sexual intercourse?

No intercourse	0
No enjoyment	1
Not very enjoyable	2
Fairly enjoyable	3
Highly enjoyable	4
Very highly enjoyable	5

9. Over the past 4 weeks when you had sexual stimulation or intercourse, how often did you ejaculate?

No sexual stimulation/intercourse	0
Almost never/never	1
A few times (much less than half the time)	2
Sometimes (about half the time)	3
Most times (much more than half the time)	4
Almost always/always	5

10. Over the past 4 weeks when you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax?

No sexual stimulation/intercourse	0
Almost never/never	1
A few times (much less than half the time)	2
Sometimes (about half the time)	3
Most times (much more than half the time)	4
Almost always/always	5

11. Over the past 4 weeks how often have you felt sexual desire?

Almost never/never	1
A few times (much less than half the time)	2
Sometimes (about half the time)	3
Most times (much more than half the time)	4
Almost always/always	5

12. Over the past 4 weeks how would you rate your level of sexual desire?

Very low/none at all	1
Low	2
Moderate	3
High	4
Very high	5

13. Over the past 4 weeks how satisfied have you been with your overall sex life?

Very dissatisfied	1
Moderately dissatisfied	2
About equally satisfied and dissatisfied	3
Moderately satisfied	4
Very satisfied	5

14. Over the past 4 weeks how satisfied have you been with your sexual relationship with your partner?

Very dissatisfied	1
Moderately dissatisfied	2
About equally satisfied and dissatisfied	3
Moderately satisfied	4
Very satisfied	5

15. Over the past 4 weeks how do you rate your confidence that you could get and keep an erection?

Very low/none at all	1
Low	2
Moderate	3
High	4
Very high	5

If erections were sufficient for sexual intercourse were these aided by any form of tablets or injections?

Yes (tablets) Yes (injections) No

If yes please insert name if known

_____

C. UCLA-EPIC Urinary Function Questionnaire

Please answer the following questions as honestly and clearly as possible.
Please Circle One Number

1. Over the **past 4 weeks**, how often have you leaked urine?

More than once a day	1
About once a day	2
More than once a week	3
About once a week	4
Rarely or never	5

2. Over the **past 4 weeks**, how often have you urinated blood?

More than once a day	1
About once a day	2
More than once a week	3
About once a week	4
Rarely or never	5

3. Over the **past 4 weeks**, how often have you had pain or burning with urination?

More than once a day	1
About once a day	2
More than once a week	3
About once a week	4
Rarely or never	5

4. Which of the following best describes your urinary control **during the last 4 weeks**?

No urinary control whatsoever	1
Frequent dribbling	2
Occasional dribbling	3
Total control	4

5. How many pads or adult diapers per day did you usually use to control leakage **during the last 4 weeks**?

None	0
1 pad per day	1
2 pads per day	2
3 or more pads per day	3

6. How big a problem, if any, has each of the following been for you **during the last 4 weeks? (Circle one number on each line)**

	No problem	Very small problem	Small problem	Moderate problem	Big problem
a. Dripping or leaking urine	0	1	2	3	4

b. Pain or burning on urination	0	1	2	3	4
c. Bleeding with urination	0	1	2	3	4
d. Weak urine stream or incomplete emptying	0	1	2	3	4
e. Waking up to urinate	0	1	2	3	4
f. Need to urinate frequently during the day	0	1	2	3	4

7. Overall, how big a problem has your urinary function been for you **during the last 4 weeks**?

No problem	1
Very small problem	2
Small problem	3
Moderate problem	4
Big problem	5

D. UCLA-EPIC Bowel Function Questionnaire

Please answer the following questions as honestly and clearly as possible.

Please Circle One Number

1. Over the **past 4 weeks**, how often have you had rectal urgency (felt like passing stool, but did not)

More than once a day	1
About once a day	2
More than once a week	3
About once a week	4
Rarely or never	5

2. Over the **past 4 weeks**, how often have you had uncontrolled leakage of stool or faeces?

More than once a day	1
About once a day	2
More than once a week	3
About once a week	4
Rarely or never	5

3. Over the **past 4 weeks**, how often have you had stools (bowel movements) that were loose or liquid (no form, watery, mushy)?

More than once a day	1
About once a day	2
More than once a week	3
About once a week	4
Rarely or never	5

4. Over the **past 4 weeks**, how often have you had bloody stools?

More than once a day	1

About once a day	2
More than once a week	3
About once a week	4
Rarely or never	5

5. Over the **past 4 weeks**, how often have your bowel movements been painful?

More than once a day	1
About once a day	2
More than once a week	3
About once a week	4
Rarely or never	5

6. Over the **past 4 weeks**, how many bowel movements have you had on a typical day?

Two or less	1
Three to four	2
Five or more	3

7. How often have you had a crampy pain in your abdomen, pelvis or rectum **during the last 4 weeks**?

More than once a day	1
About once a day	2
More than once a week	3
About once a week	4
Rarely or never	5

8. How big a problem, if any, has each of the following been for you **during the last 4 weeks? (Circle one number on each line)**

	No problem	Very small problem	Small problem	Moderate problem	Big problem
a. Urgency to have a bowel movement	0	1	2	3	4
b. Increased frequency of bowel movements	0	1	2	3	4
c. Watery bowel movements	0	1	2	3	4
d. Losing control of your stools	0	1	2	3	4
e. Bloody stools	0	1	2	3	4
f. Abdominal/pelvic /rectal pain	0	1	2	3	4

7. Overall, how big a problem has your bowel habits been for you **during the last 4 weeks**?

No problem	1
Very small problem	2
Small problem	3
Moderate problem	4
Big problem	5

End of Questionnaire

Please use this page for any additional comments you feel may help or you wish to portray.

10.3 Outcomes of FORECAST Trial – FS-HIFU and Cryotherapy

10.3.1 Table 49 – Functional outcomes– Baseline scores of functional questionnaires and 12 months. Baseline scores of functional questionnaires and then follow up at 4 weeks, 3 months, 6 months, 9 months and 12 months.

	Mean	Median	SD
Baseline IPSS (n=18)	9.67	8.00	5.531
Baseline IPSS QOL	1.44	1.00	1.247
Baseline IIEF-15 (n=18)	21.61	15.00	19.162
Baseline IIEF -1	1.978	.50	1.50
Baseline IIEF-2	1.33	.00	1.910
Baseline IIEF-3	1.17	.00	1.886
Baseline IIEF-4	1.06	.00	1.862
Baseline IIEF – 5 (n=16)	1.69	1.00	1.352
Baseline UCLA EPIC URINE (n=17)	23.53	23.00	3.145
Baseline UCLA EPIC URINE 1	4.65	5.00	.862
Baseline UCLA EPIC URINE 4	3.76	4.00	.437
Baseline UCLA EPIC URINE 5	.00	.00	.000
Baseline UCLA EPIC BOWEL (n=18)	24.17	23.00	3.808

Baseline UCLA EPIC BOWEL 1	4.72	5.00	.752
Baseline UCLA EPIC BOWEL 2	5.00	5.00	.000
Baseline UCLA EPIC BOWEL 8D	.22	.00	.428
4 WEEK IPSS (n=19)	11.47	10.00	6.670
4WK IPSS QOL	2.32	2.00	1.293
4 WK IIEF-15	16.79	13.00	12.331
4 WK IIEF -1	1.05	.00	1.715
4 WK IIEF-2	.47	.00	.964
4 WK IIEF-3	.26	.00	.733
4 WK IIEF-4	.26	.00	.733
4 WK IIEF - 5	1.21	1.00	.713
4 WK UCLA EPIC URINE	24.47	24.00	3.687
4 WK UCLA EPIC URINE 1	4.28	5.00	1.018
4 WK UCLA EPIC URINE 4	3.37	3.00	.597
4 WK UCLA EPIC URINE 5	.21	.00	.419
4 WK UCLA EPIC BOWEL	25.11	25.00	5.043
4 WK UCLA EPIC BOWEL 1	4.58	5.00	.838
4 WK UCLA EPIC BOWEL 2	4.74	5.00	.733
4 WK UCLA EPIC BOWEL 8D	.26	.00	.562
3 MTH IPSS (n=18)	11.33	11.50	6.834

3 MTH IPSS QOL	2.00	2.00	1.138
3 MTH IIEF-15	18.72	13.50	15.017
3 MTH IIEF -1	.94	.00	1.474
3 MTH IIEF-2	.78	.00	1.114
3 MTH IIEF-3	.61	.00	1.037
3 MTH IIEF-4	.61	.00	1.037
3 MTH IIEF - 5	1.44	1.00	.984
3 MTH UCLA EPIC URINE	23.39	23.50	4.642
3 MTH UCLA EPIC URINE 1	4.39	5.00	.850
3 MTH UCLA EPIC BOWEL 2 (n=17)	4.82	5.00	.529
3 MTH UCLA EPIC URINE 4 (n=17)	3.59	4.00	.507
3 MTH UCLA EPIC URINE 5 (n=18)	.06	.00	.236
3 MTH UCLA EPIC BOWEL (n=17)	25.29	24.00	6.039
3 MTH UCLA EPIC BOWEL 1 (n=17)	4.82	5.00	.393
3 MTH UCLA EPIC BOWEL 8D (n=16)	.31	.00	.793
6 MTH IPSS (n=19)	9.95	9.00	5.864
6 MTH IPSS QOL	1.95	2.00	1.129
6 MTH IIEF-15	19.42	17.00	12.777

6 MTH IIEF -1	2.68	1.00	7.219
6 MTH IIEF-2	1.00	1.00	1.374
6 MTH IIEF-3	.79	.00	1.357
6 MTH IIEF-4	.74	.00	1.195
6 MTH IIEF - 5	1.37	1.00	.895
6 MTH UCLA EPIC URINE (N=19)	24.42	24.00	3.906
6 MTH UCLA EPIC URINE 1 (n=18)	4.67	5.00	.594
6 MTH UCLA EPIC URINE 4	3.63	4.00	.496
6 MTH UCLA EPIC URINE 5	.00	.00	.000
6 MTH UCLA EPIC BOWEL (N=18)	24.00	22.00	8.863
6 MTH UCLA EPIC BOWEL 1 (n=18)	4.83	5.00	.383
6 MTH UCLA EPIC BOWEL 2 (n=18)	4.89	5.00	.323
6 MTH UCLA EPIC BOWEL 8D	.39	.00	.778
12 MTH IPSS (N=8)	11.88	11.50	6.379
12 MTH IPSS QOL	2.13	2.50	1.126
12 MTH IIEF-15	15.63	13.50	7.999
12 MTH IIEF -1	.50	.00	.756
12 MTH IIEF-2	.38	.00	.518

12 MTH IIEF-3	.25	.00	.707
12 MTH IIEF-4	.13	.00	.354
12 MTH IIEF - 5	1.13	1.00	.354
12 MTH UCLA EPIC URINE	26.13	25.00	3.944
12 MTH UCLA EPIC URINE 1	4.63	5.00	.518
12 MTH UCLA EPIC URINE 4	3.50	3.50	.535
12 MTH UCLA EPIC URINE 5	.00	.00	.000
12 MTH UCLA EPIC BOWEL	25.63	24.50	6.501
12 MTH UCLA EPIC BOWEL 1	4.75	5.00	.463
12 MTH UCLA EPIC BOWEL 2	4.88	5.00	.354
12 MTH UCLA EPIC BOWEL 8D	.50	.00	.756

10.3.2 Table 50 – Paired t –test Functional outcomes – Baseline scores of functional questionnaires compared with follow up at 4 weeks, 3 months, 6 months, 9 months and 12 months.

		Paired Differences					
					95% Confidence Interval of the Difference		
		Mean	Std. Deviation	Std. Error Mean	Lower	Upper	p-value
Pair 1	Baseline IPSS - 4 WEEK IPSS	-2.000	5.134	1.210	-4.553	.553	.117
Pair 2	Baseline IPSS - 3 MTH IPSS	-1.667	5.509	1.299	-4.406	1.073	.217
Pair 3	Baseline IPSS - 6 MTH IPSS	-.611	7.724	1.821	-4.452	3.230	.741
Pair 4	Baseline IPSS - 9 MTH IPSS	-.692	4.516	1.253	-3.422	2.037	.591
Pair 5	Baseline IPSS - 12 MTH IPSS	-.500	6.481	2.291	-5.918	4.918	.833
Pair 6	Baseline IPSS QOL - 4WK IPSS QOL	-.889	1.711	.403	-1.740	-.038	.042
Pair 7	Baseline IPSS QOL - 3 MTH IPSS QOL	-.556	1.542	.364	-1.323	.211	.145
Pair 8	Baseline IPSS QOL - 6 MTH IPSS QOL	-.500	1.465	.345	-1.229	.229	.166
Pair 9	Baseline IPSS QOL - 9 MTH IPSS QOL	-.692	.630	.175	-1.073	-.311	.002

Pair 10	Baseline IPSS QOL - 12 MTH IPSS QOL	-.625	1.061	.375	-1.512	.262	.140
Pair 11	Baseline IIEF-15 - 4 WK IIEF-15	5.611	14.017	3.304	-1.360	12.582	.108
Pair 12	Baseline IIEF-15 - 3 MTH IIEF-15	2.889	13.239	3.121	-3.695	9.473	.368
Pair 13	Baseline IIEF-15 - 6 MTH IIEF-15	1.944	21.618	5.095	-8.806	12.695	.707
Pair 14	Baseline IIEF-15 - 9 MTH IIEF-15	4.833	22.478	6.489	-9.448	19.115	.472
Pair 15	Baseline IIEF-15 - 12 MTH IIEF-15	6.750	17.144	6.061	-7.583	21.083	.302
Pair 16	Baseline IIEF -1 - 4 WK IIEF -1	.667	1.138	.268	.101	1.232	.024
Pair 17	Baseline IIEF -1 - 3 MTH IIEF -1	.556	1.294	.305	-.088	1.199	.086
Pair 18	Baseline IIEF -1 - 6 MTH IIEF -1	-1.278	7.940	1.871	-5.226	2.670	.504
Pair 19	Baseline IIEF -1 - 9 MTH IIEF -1	.917	1.782	.514	-.215	2.049	.102

Pair 20	Baseline IIEF -1 - 12 MTH IIEF -1	.875	1.356	.479	-.259	2.009	.111
Pair 21	Baseline IIEF-2 - 4 WK IIEF-2	.889	1.410	.332	.188	1.590	.016
Pair 22	Baseline IIEF-2 - 3 MTH IIEF-2	.556	1.149	.271	-.016	1.127	.056
Pair 23	Baseline IIEF-2 - 6 MTH IIEF-2	.333	2.567	.605	-.943	1.610	.589
Pair 24	Baseline IIEF-2 - 9 MTH IIEF-2	.833	1.801	.520	-.311	1.977	.137
Pair 25	Baseline IIEF-2 - 12 MTH IIEF-2	.875	1.642	.581	-.498	2.248	.175
Pair 26	Baseline IIEF-3 - 4 WK IIEF-3	.889	1.530	.361	.128	1.650	.025
Pair 27	Baseline IIEF-3 - 3 MTH IIEF-3	.556	1.199	.283	-.041	1.152	.066
Pair 28	Baseline IIEF-3 - 6 MTH IIEF-3	.333	2.612	.616	-.966	1.632	.595
Pair 29	Baseline IIEF-3 - 9 MTH IIEF-3	.917	1.505	.434	-.040	1.873	.059
Pair 30	Baseline IIEF-3 - 12 MTH IIEF-3	.750	1.389	.491	-.411	1.911	.170

Pair 31	Baseline IIEF-4 - 4 WK IIEF-4	.778	1.517	.358	.023	1.532	.044
Pair 32	Baseline IIEF-4 - 3 MTH IIEF-4	.444	1.199	.283	-.152	1.041	.134
Pair 33	Baseline IIEF-4 - 6 MTH IIEF-4	.278	2.469	.582	-.950	1.505	.639
Pair 34	Baseline IIEF-4 - 9 MTH IIEF-4	.667	1.435	.414	-.245	1.579	.136
Pair 35	Baseline IIEF-4 - 12 MTH IIEF-4	.750	1.488	.526	-.494	1.994	.197
Pair 36	Baseline IIEF - 5 - 4 WK IIEF - 5	.500	1.265	.316	-.174	1.174	.135
Pair 37	Baseline IIEF - 5 - 3 MTH IIEF - 5	.250	.577	.144	-.058	.558	.104
Pair 38	Baseline IIEF - 5 - 6 MTH IIEF - 5	.250	1.732	.433	-.673	1.173	.572
Pair 39	Baseline IIEF - 5 - 9 MTH IIEF - 5	.700	1.703	.539	-.518	1.918	.226
Pair 40	Baseline IIEF - 5 - 12 MTH IIEF - 5	.429	.787	.297	-.299	1.156	.200
Pair 41	Baseline UCLA EPIC URINE - 4	-1.000	4.757	1.154	-3.446	1.446	.399

	WK UCLA EPIC URINE						
Pair 42	Baseline UCLA EPIC URINE - 3 MTH UCLA EPIC URINE	.059	3.929	.953	-1.961	2.079	.952
Pair 43	Baseline UCLA EPIC URINE - 6 MTH UCLA EPIC URINE	-.941	3.682	.893	-2.834	.952	.308
Pair 44	Baseline UCLA EPIC URINE - 9 MTH UCLA EPIC URINE	.667	5.015	1.448	-2.520	3.853	.654
Pair 45	Baseline UCLA EPIC URINE - 12 MTH UCLA EPIC URINE	-1.875	3.523	1.246	-4.820	1.070	.176
Pair 46	Baseline UCLA EPIC URINE 1 - 4 WK UCLA EPIC URINE 1	.438	1.031	.258	-.112	.987	.110
Pair 47	Baseline UCLA EPIC URINE 1 - 3 MTH UCLA EPIC URINE 1	.294	1.047	.254	-.244	.832	.264

Pair 48	Baseline UCLA EPIC URINE 1 - 6 MTH UCLA EPIC URINE 1	-.125	1.088	.272	-.705	.455	.652
Pair 49	Baseline UCLA EPIC URINE 4 - 9 MTH UCLA EPIC URINE 1	-.583	.793	.229	-1.087	-.080	.027
Pair 50	Baseline UCLA EPIC URINE 1 - 12 MTH UCLA EPIC URINE 1	.250	.463	.164	-.137	.637	.170
Pair 51	Baseline UCLA EPIC URINE 4 - 4 WK UCLA EPIC URINE 4	.412	.712	.173	.046	.778	.030
Pair 52	Baseline UCLA EPIC URINE 4 - 3 MTH UCLA EPIC URINE 4	.250	.577	.144	-.058	.558	.104
Pair 53	Baseline UCLA EPIC URINE 4 - 6 MTH UCLA	.118	.697	.169	-.241	.476	.496

	EPIC URINE 4						
Pair 54	Baseline UCLA EPIC URINE 4 - 9 MTH UCLA EPIC URINE 4	.250	.622	.179	-.145	.645	.191
Pair 55	Baseline UCLA EPIC URINE 4 - 12 MTH UCLA EPIC URINE 4	.375	.744	.263	-.247	.997	.197
Pair 56	Baseline UCLA EPIC URINE 5 - 4 WK UCLA EPIC URINE 5	-.235	.437	.106	-.460	-.010	.041
Pair 57	Baseline UCLA EPIC URINE 5 - 3 MTH UCLA EPIC URINE 5	-.059	.243	.059	-.184	.066	.332
Pair 61	Baseline UCLA EPIC BOWEL - 4 WK UCLA EPIC BOWEL	-.944	4.304	1.015	-3.085	1.196	.365
Pair 62	Baseline UCLA EPIC BOWEL - 3	-1.176	4.927	1.195	-3.710	1.357	.340

	MTH UCLA EPIC BOWEL						
Pair 63	Baseline UCLA EPIC BOWEL - 6 MTH UCLA EPIC BOWEL	.889	8.288	1.954	-3.233	5.010	.655
Pair 64	Baseline UCLA EPIC BOWEL - 9 MTH UCLA EPIC BOWEL	-.167	5.078	1.466	-3.393	3.060	.912
Pair 65	Baseline UCLA EPIC BOWEL - 12 MTH UCLA EPIC BOWEL	-2.625	5.208	1.841	-6.979	1.729	.197
Pair 66	Baseline UCLA EPIC BOWEL 1 - 4 WK UCLA EPIC BOWEL 1	.111	1.183	.279	-.477	.699	.695
Pair 67	Baseline UCLA EPIC BOWEL 1 - 3 MTH UCLA EPIC BOWEL 1	-.118	.928	.225	-.595	.359	.608
Pair 68	Baseline UCLA EPIC BOWEL 1 - 6 MTH UCLA	-.118	.857	.208	-.559	.323	.579

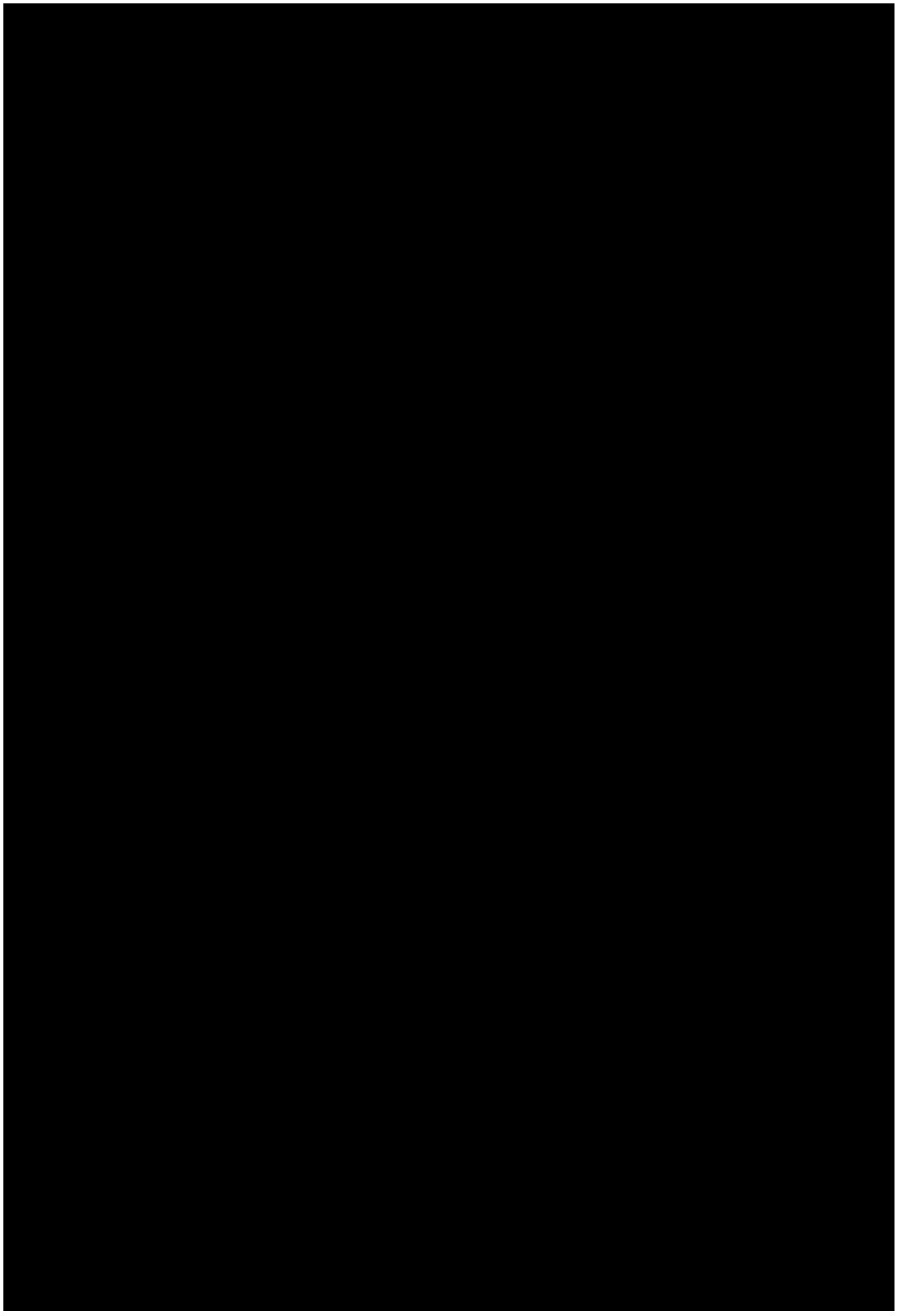
	EPIC BOWEL 1						
Pair 69	Baseline UCLA EPIC BOWEL 1 - 9 MTH UCLA EPIC BOWEL 1	-.083	.996	.288	-.716	.550	.777
Pair 70	Baseline UCLA EPIC BOWEL 1 - 12 MTH UCLA EPIC BOWEL 1	.250	.463	.164	-.137	.637	.170
Pair 71	Baseline UCLA EPIC BOWEL 2 - 4 WK UCLA EPIC BOWEL 2	.278	.752	.177	-.096	.652	.135
Pair 72	Baseline UCLA EPIC BOWEL 2 - 3 MTH UCLA EPIC BOWEL 2	.176	.529	.128	-.095	.448	.188
Pair 73	Baseline UCLA EPIC BOWEL 2 - 6 MTH UCLA EPIC BOWEL 2	.118	.332	.081	-.053	.288	.163
Pair 74	Baseline UCLA EPIC	.333	.778	.225	-.161	.828	.166

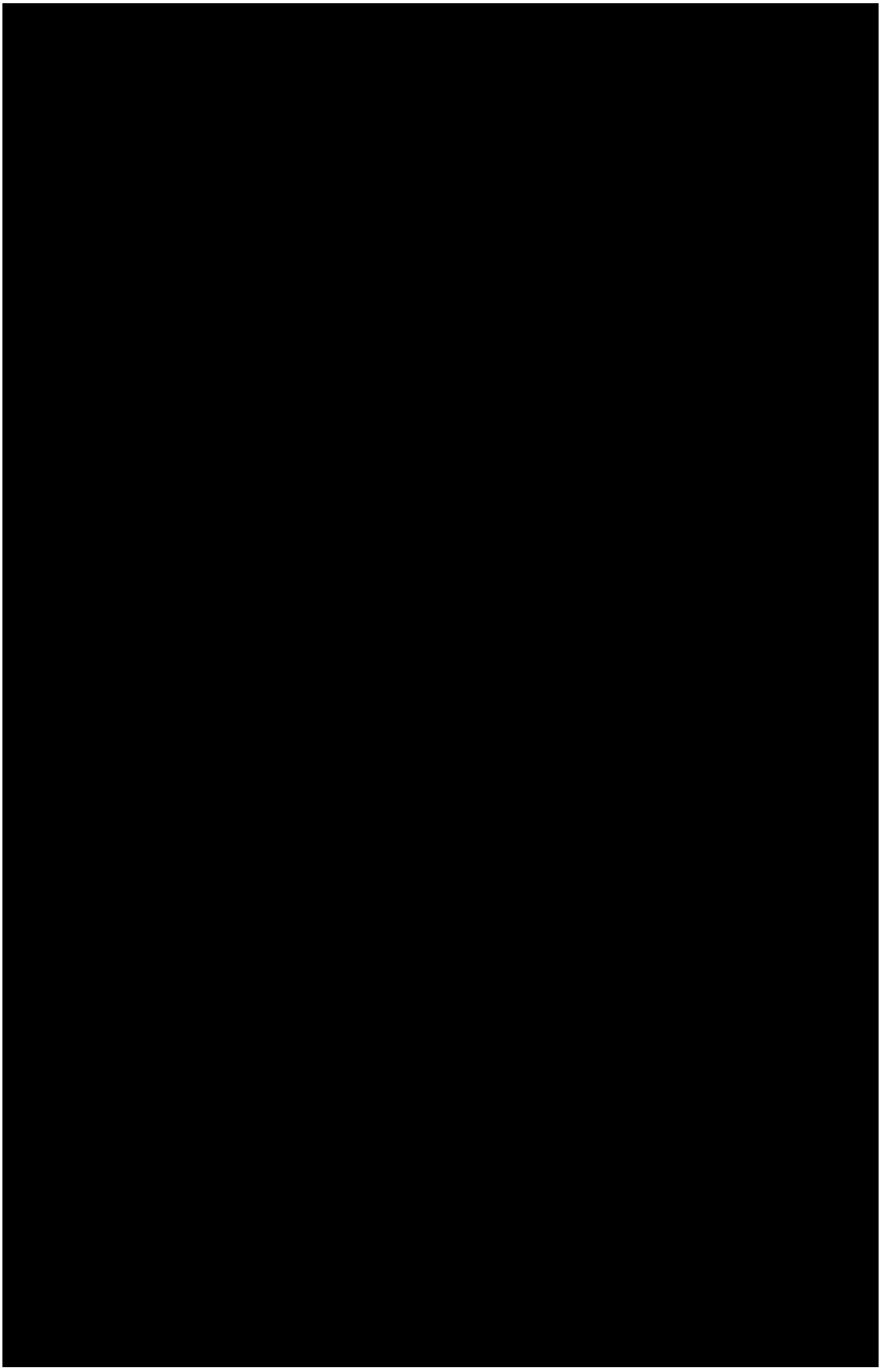
	BOWEL 2 - 9 MTH UCLA EPIC BOWEL 2						
Pair 75	Baseline UCLA EPIC BOWEL 2 - 12 MTH UCLA EPIC BOWEL 2	.125	.354	.125	-.171	.421	.351
Pair 76	Baseline UCLA EPIC BOWEL 8D - 4 WK UCLA EPIC BOWEL 8D	-.056	.639	.151	-.373	.262	.717
Pair 77	Baseline UCLA EPIC BOWEL 8D - 3 MTH UCLA EPIC BOWEL 8D	-.063	.929	.232	-.557	.432	.791
Pair 78	Baseline UCLA EPIC BOWEL 8D - 6 MTH UCLA EPIC BOWEL 8D	-.176	.883	.214	-.630	.277	.422
Pair 79	Baseline UCLA EPIC BOWEL 8D - 9 MTH UCLA EPIC BOWEL 8D	-.083	.289	.083	-.267	.100	.339

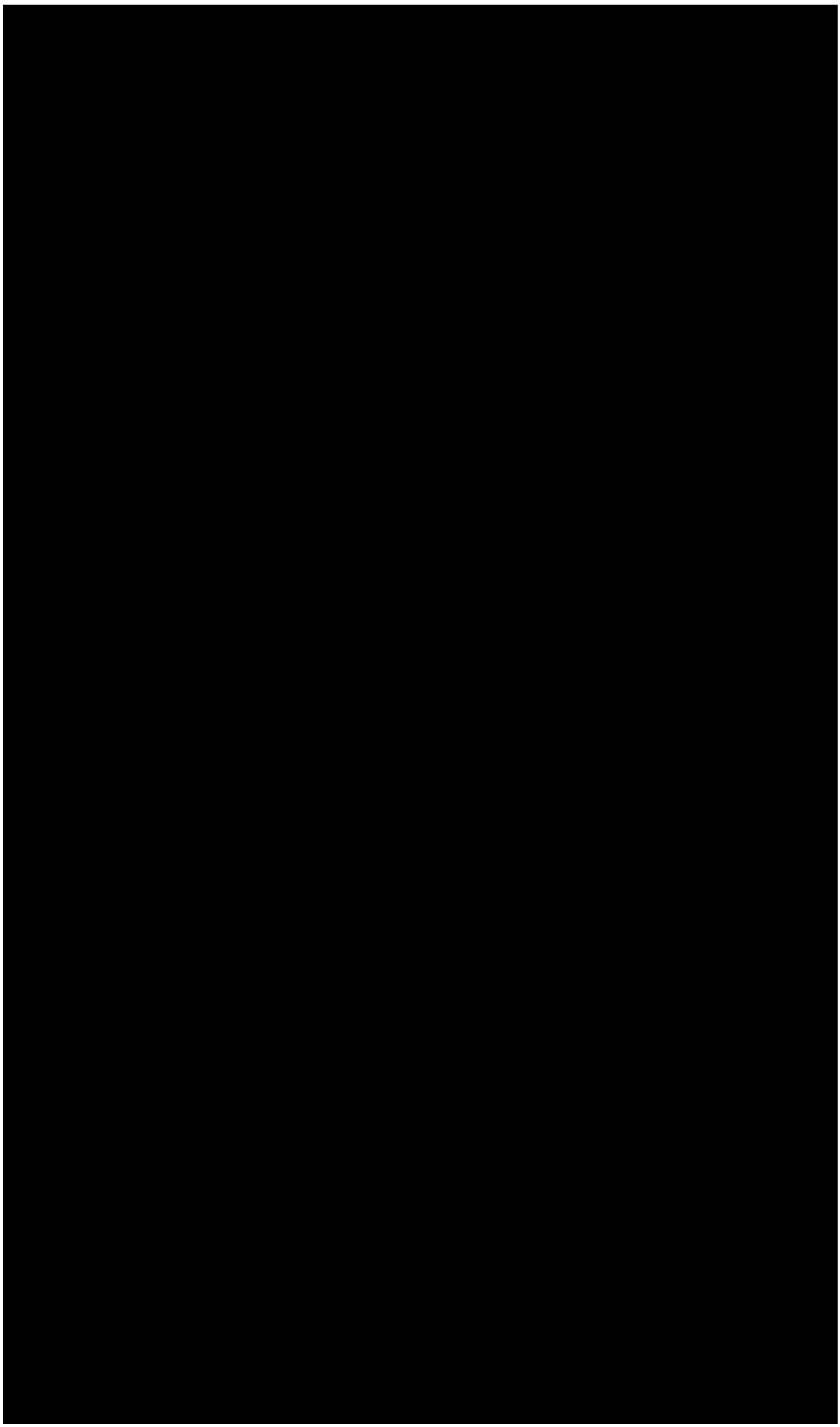
Pair 80	Baseline UCLA EPIC BOWEL 8D - 12 MTH UCLA EPIC BOWEL 8D	-.500	.756	.267	-1.132	.132	.104

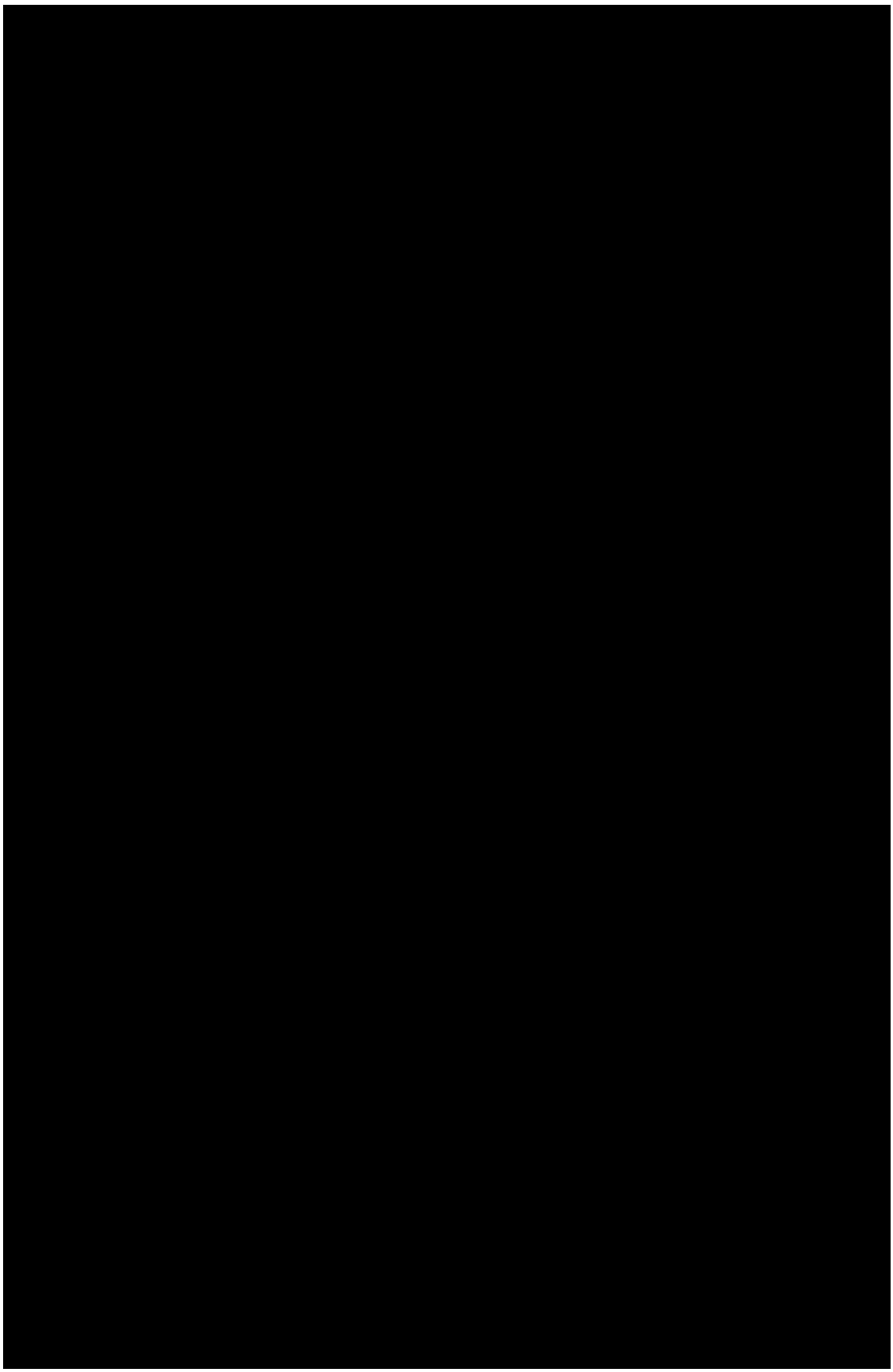
Chapter 11 Publications and Abstracts

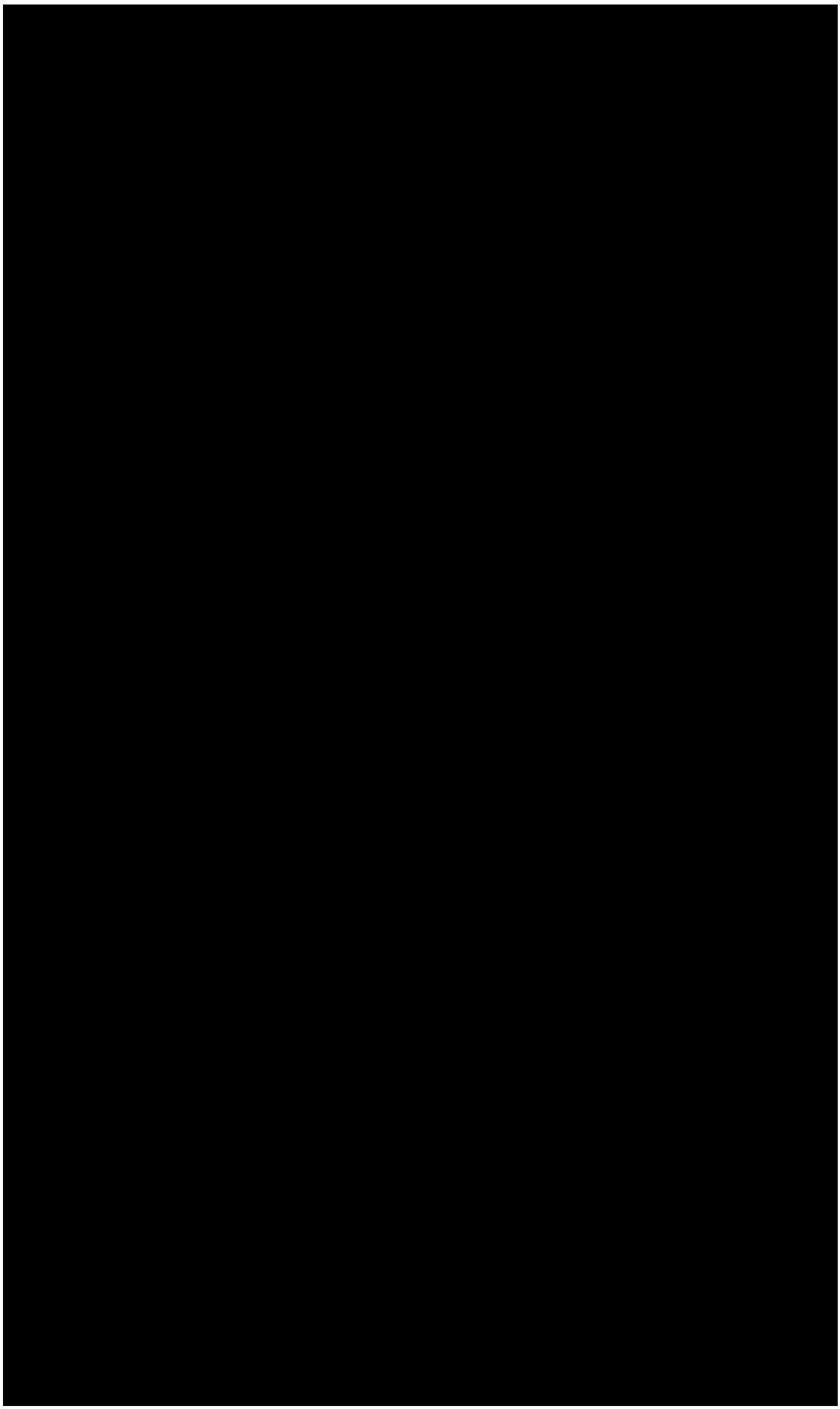
11.1 Role of focal salvage ablative therapy in localised radiorecurrent prostate cancer

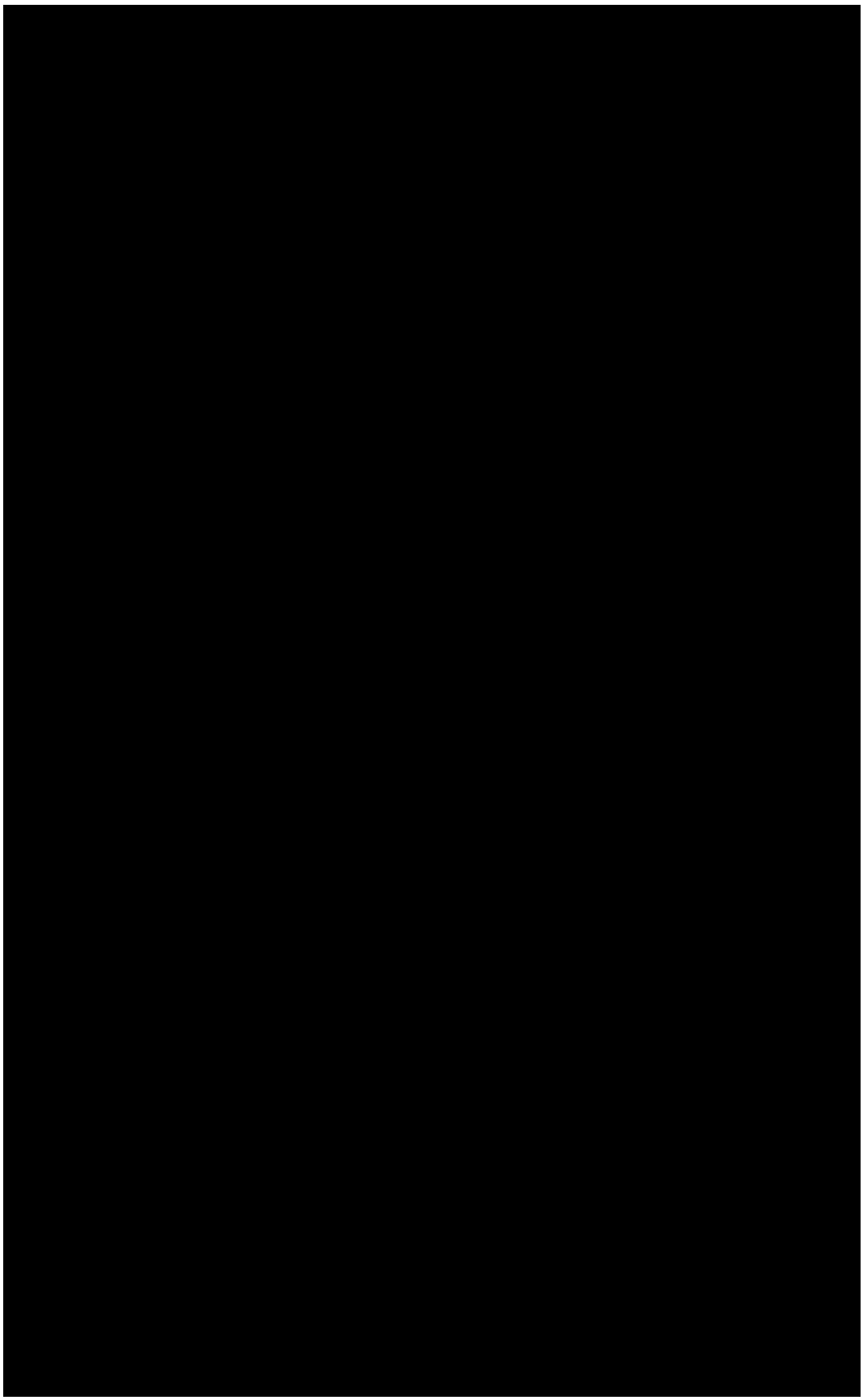


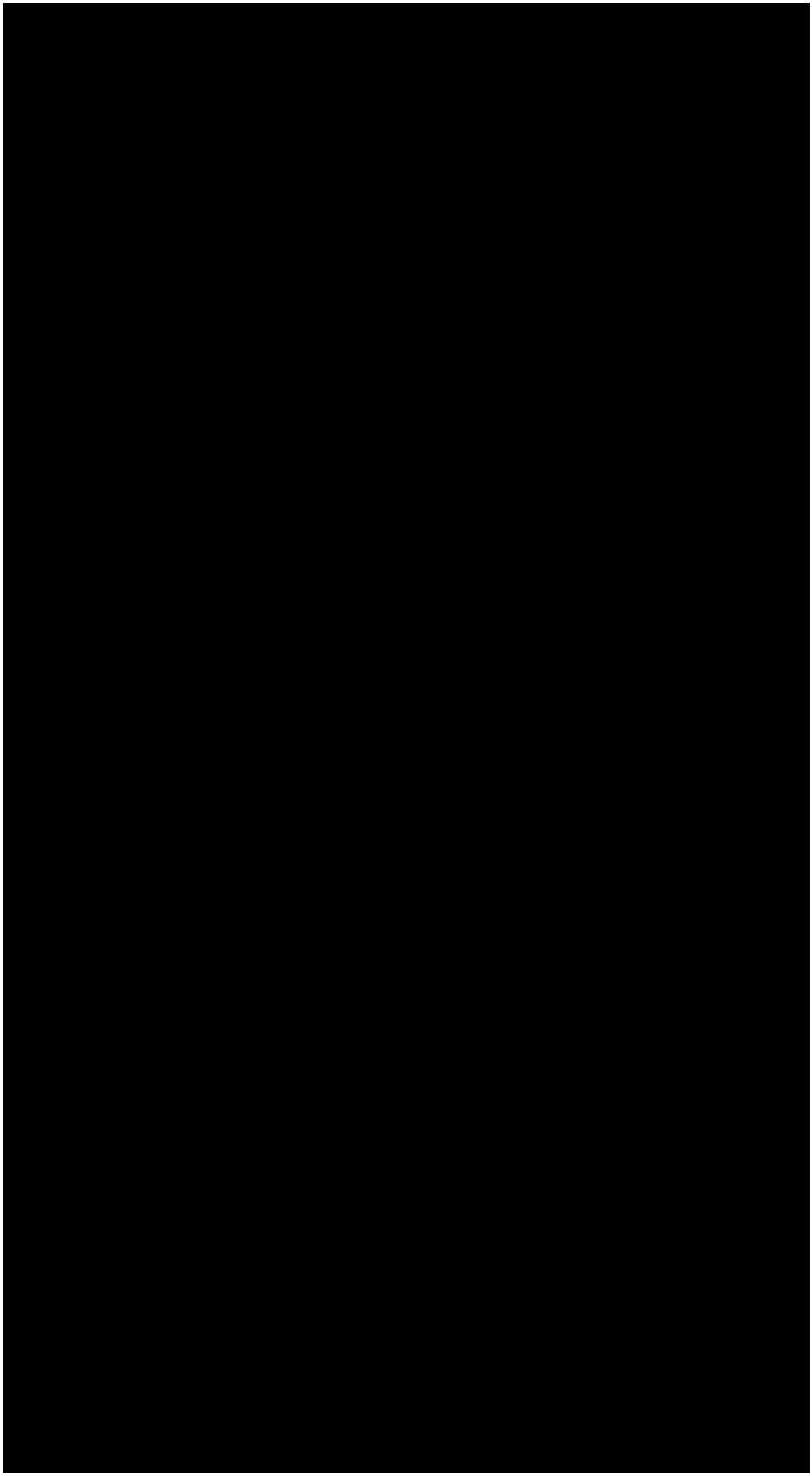


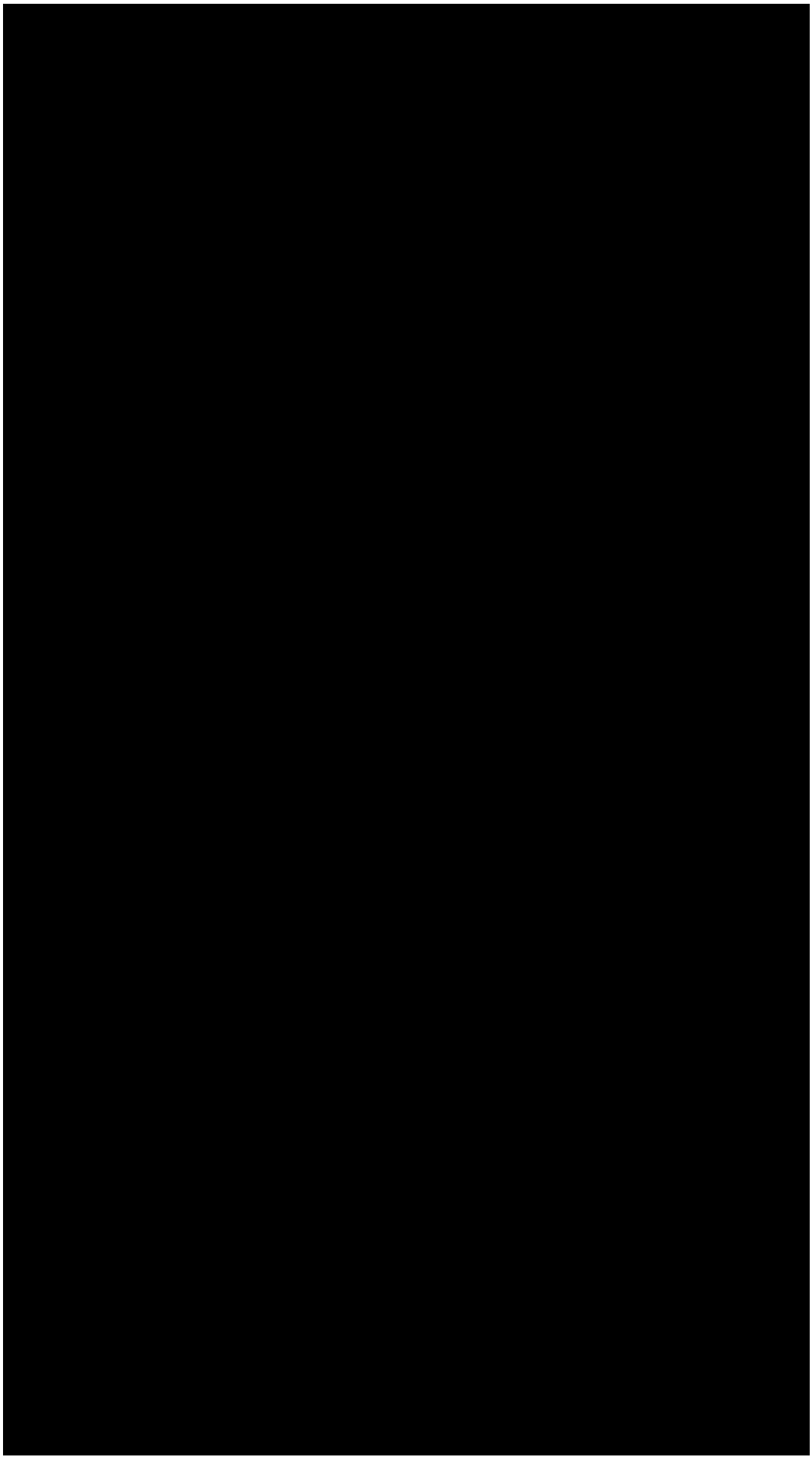




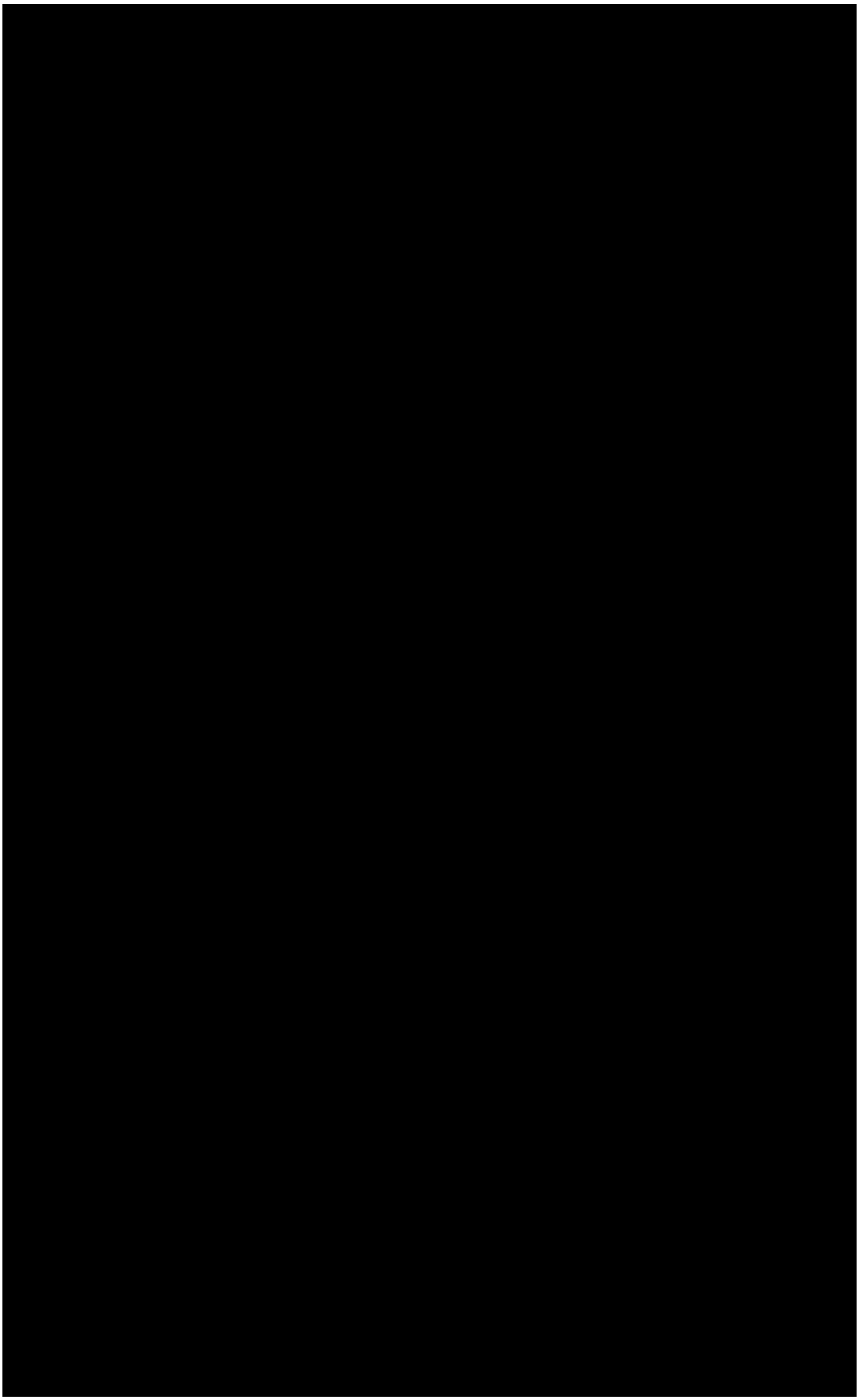


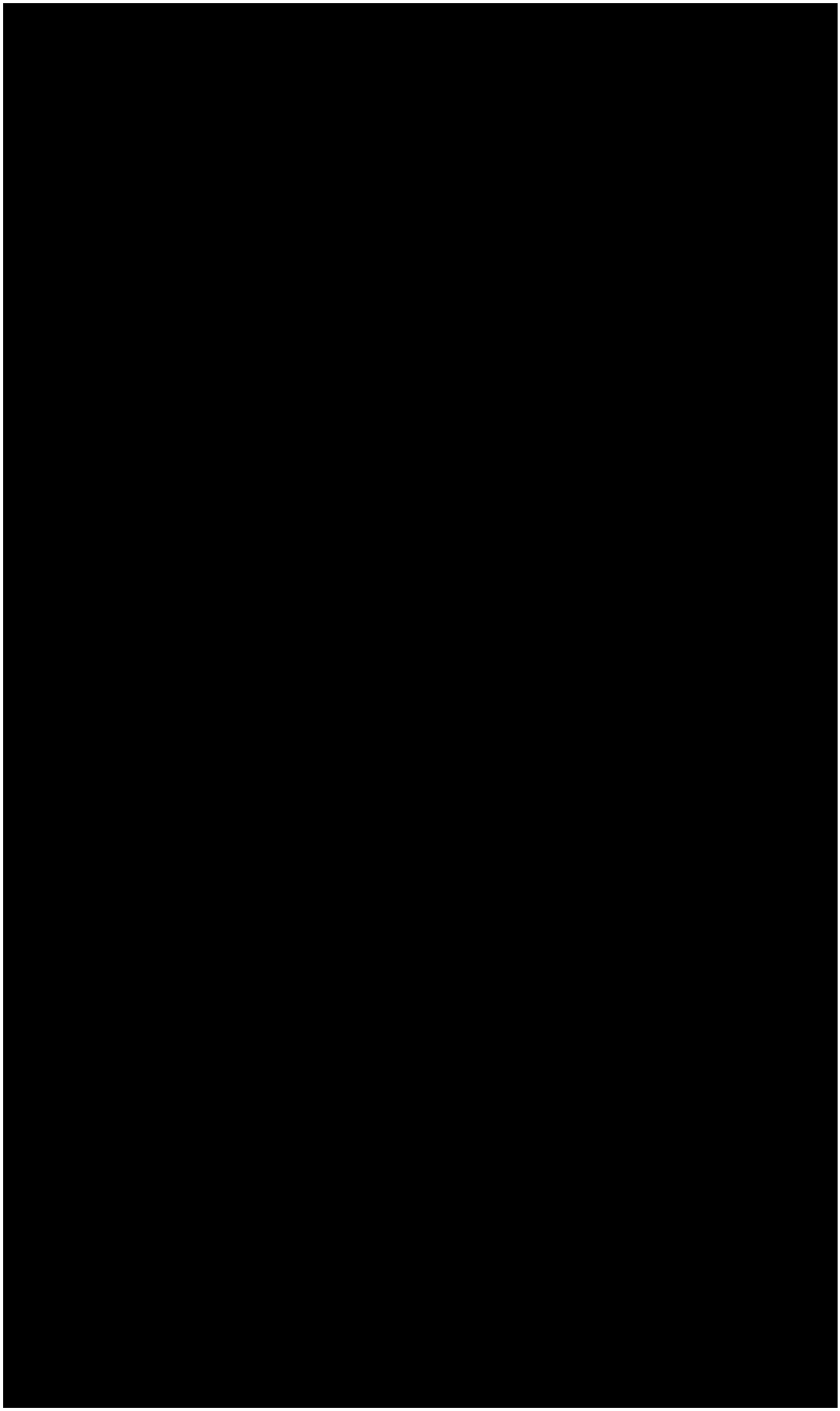


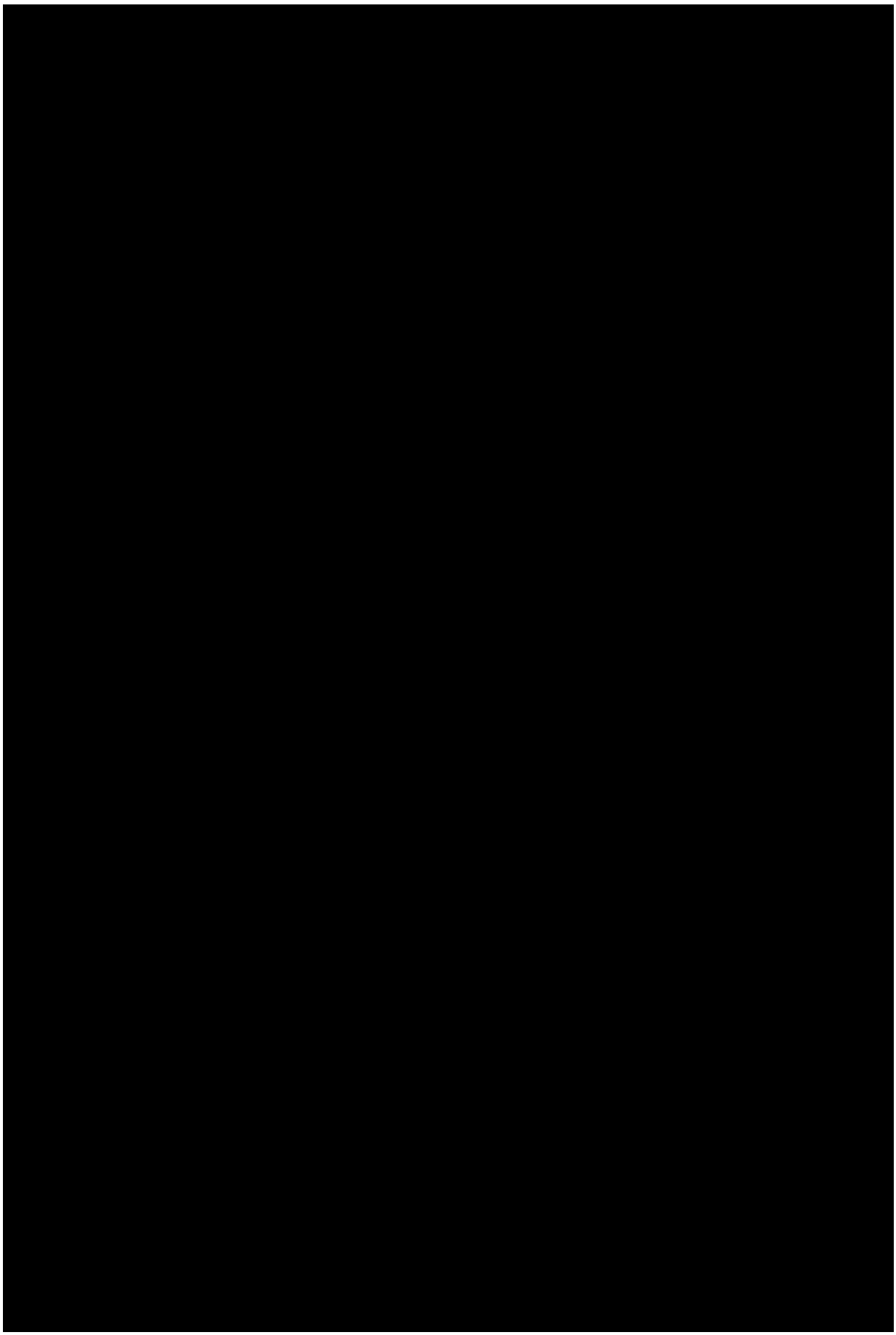


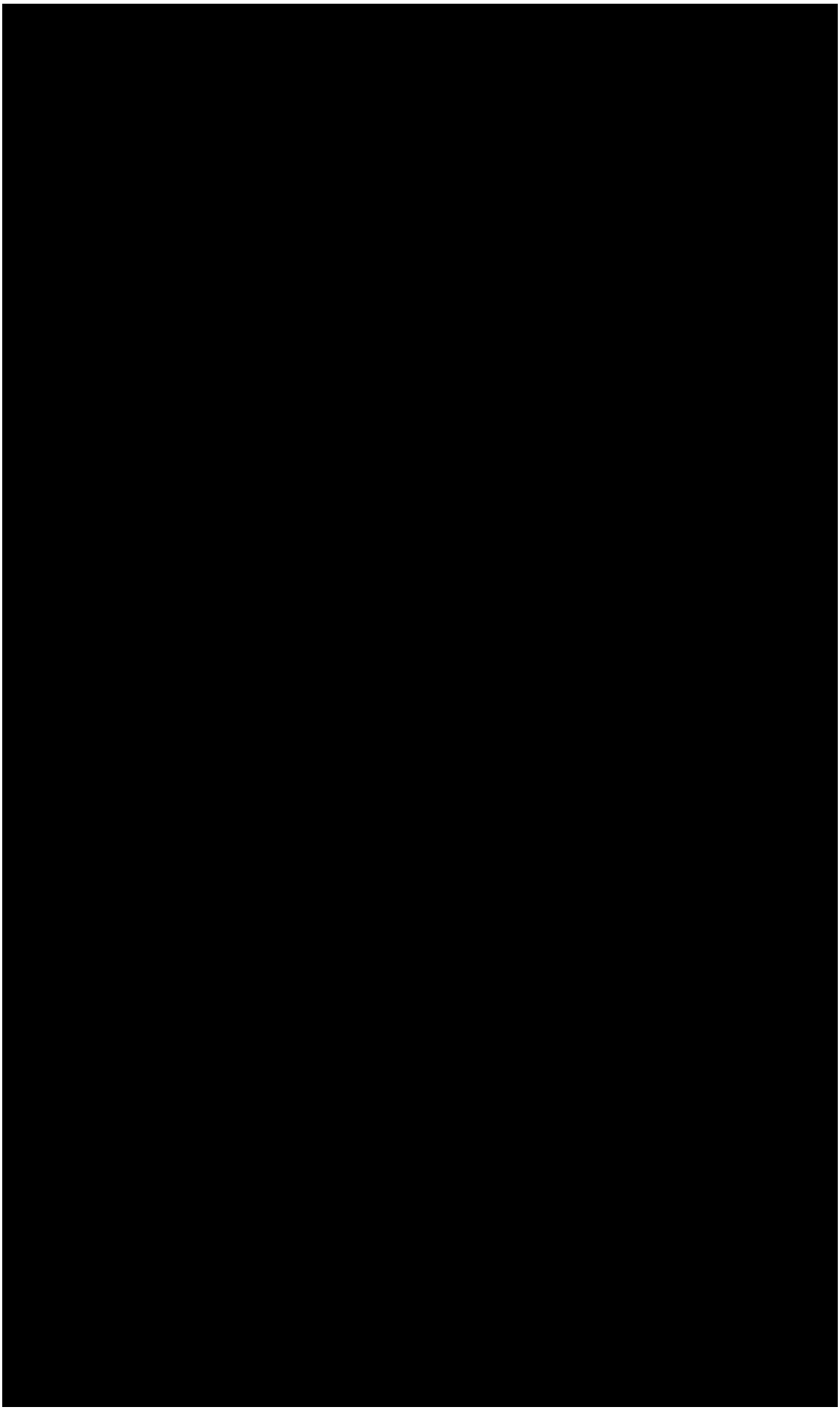


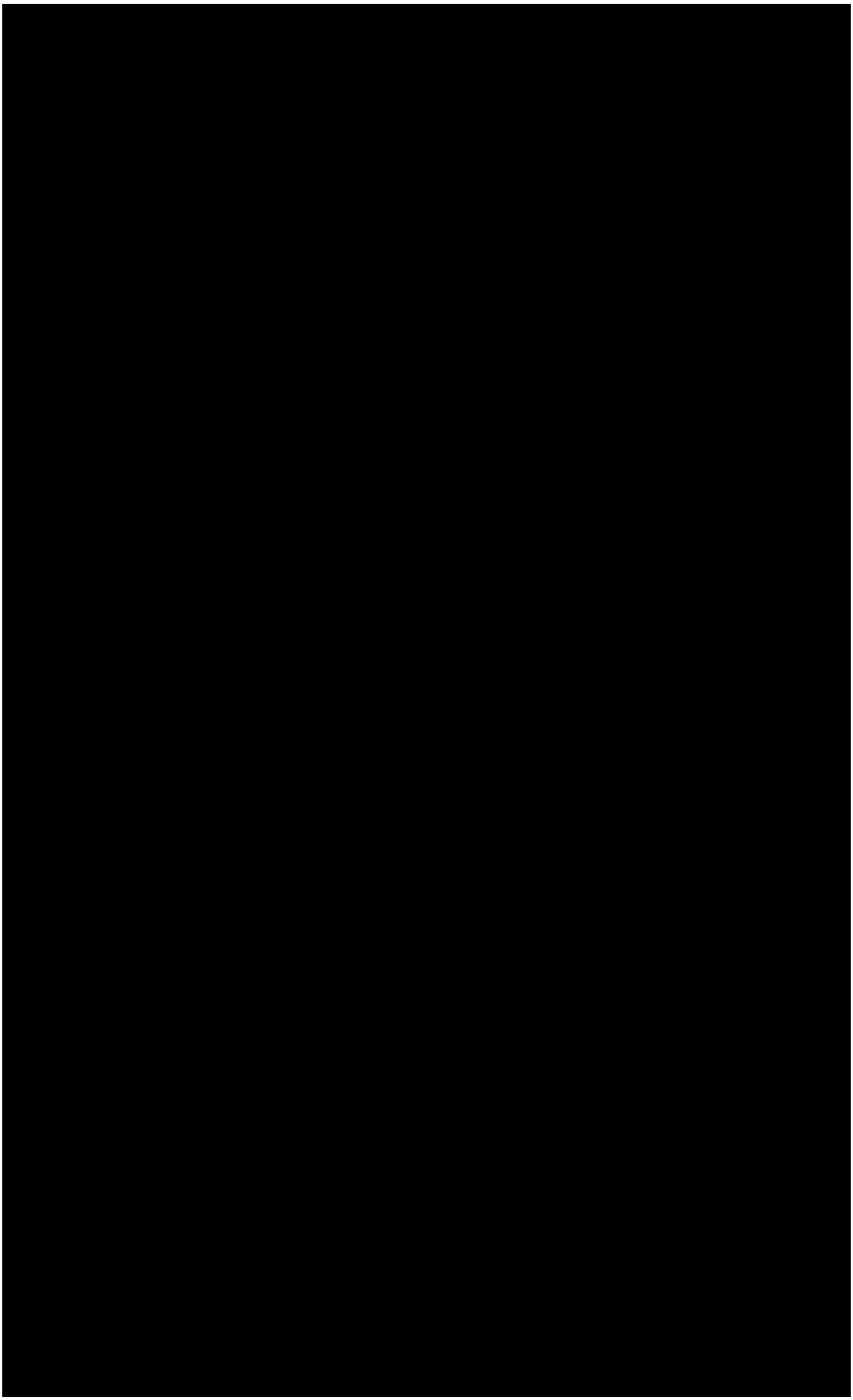
11.2 Biopsy Strategies for selecting patients for focal therapy for prostate cancer

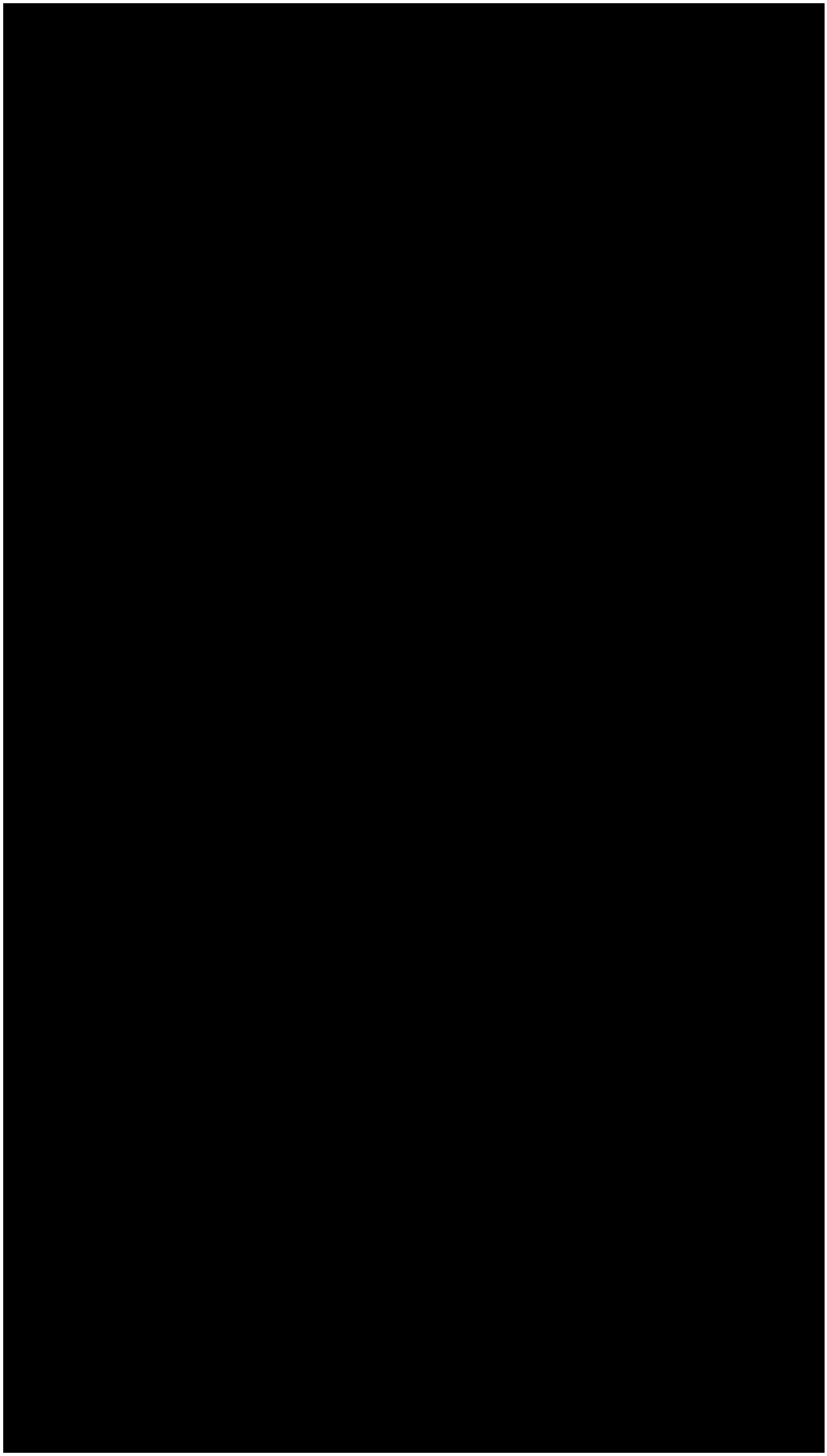


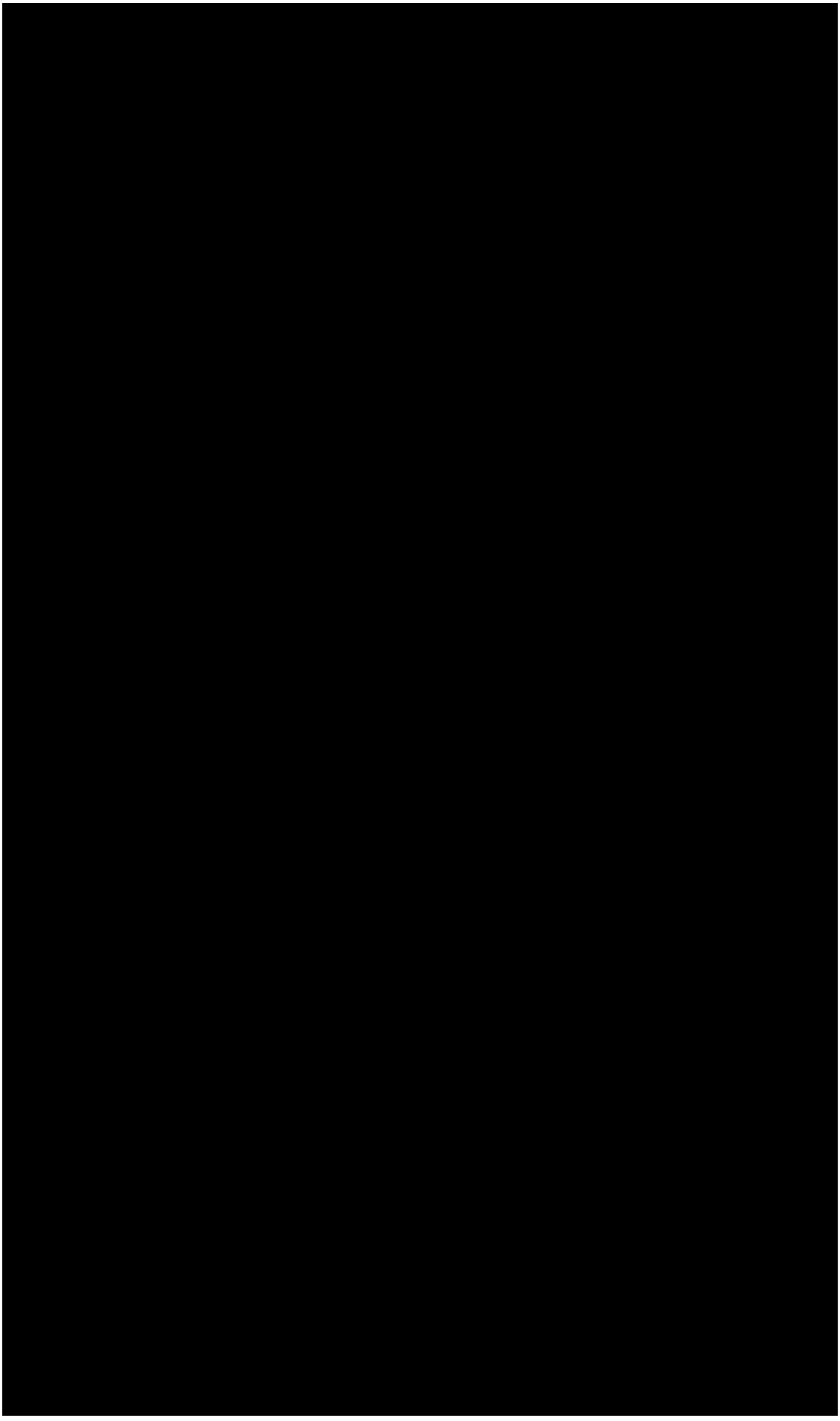


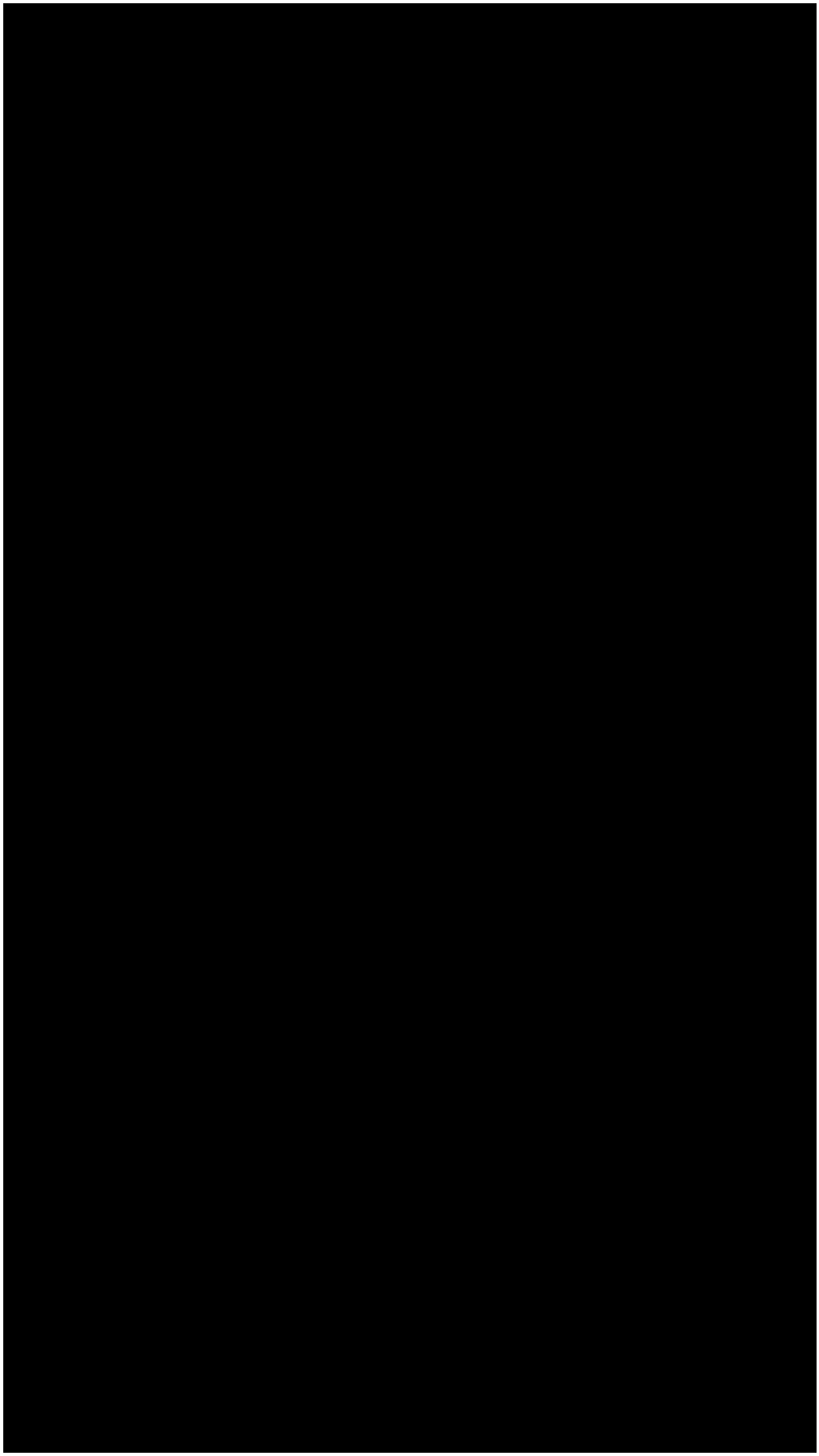


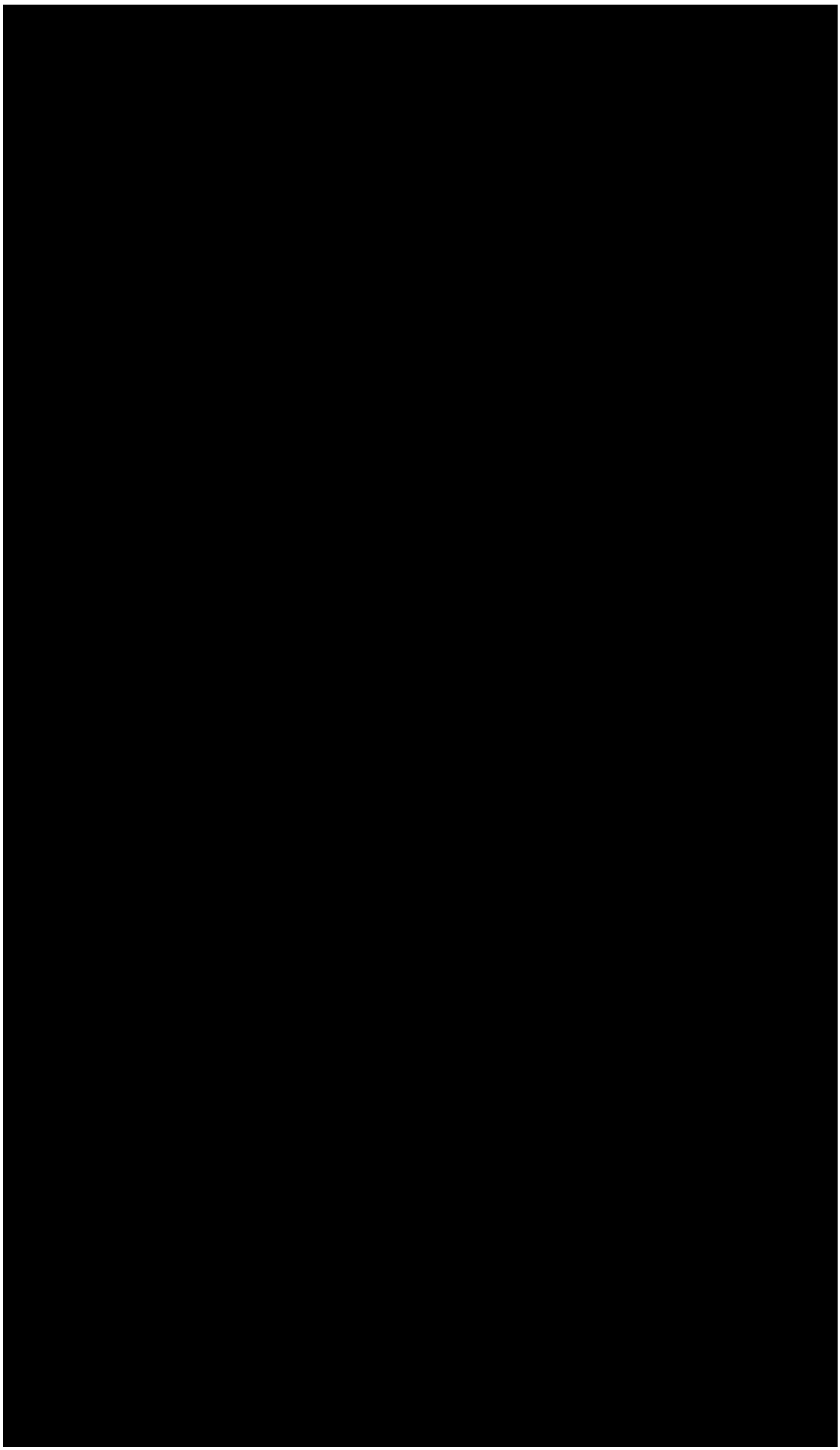




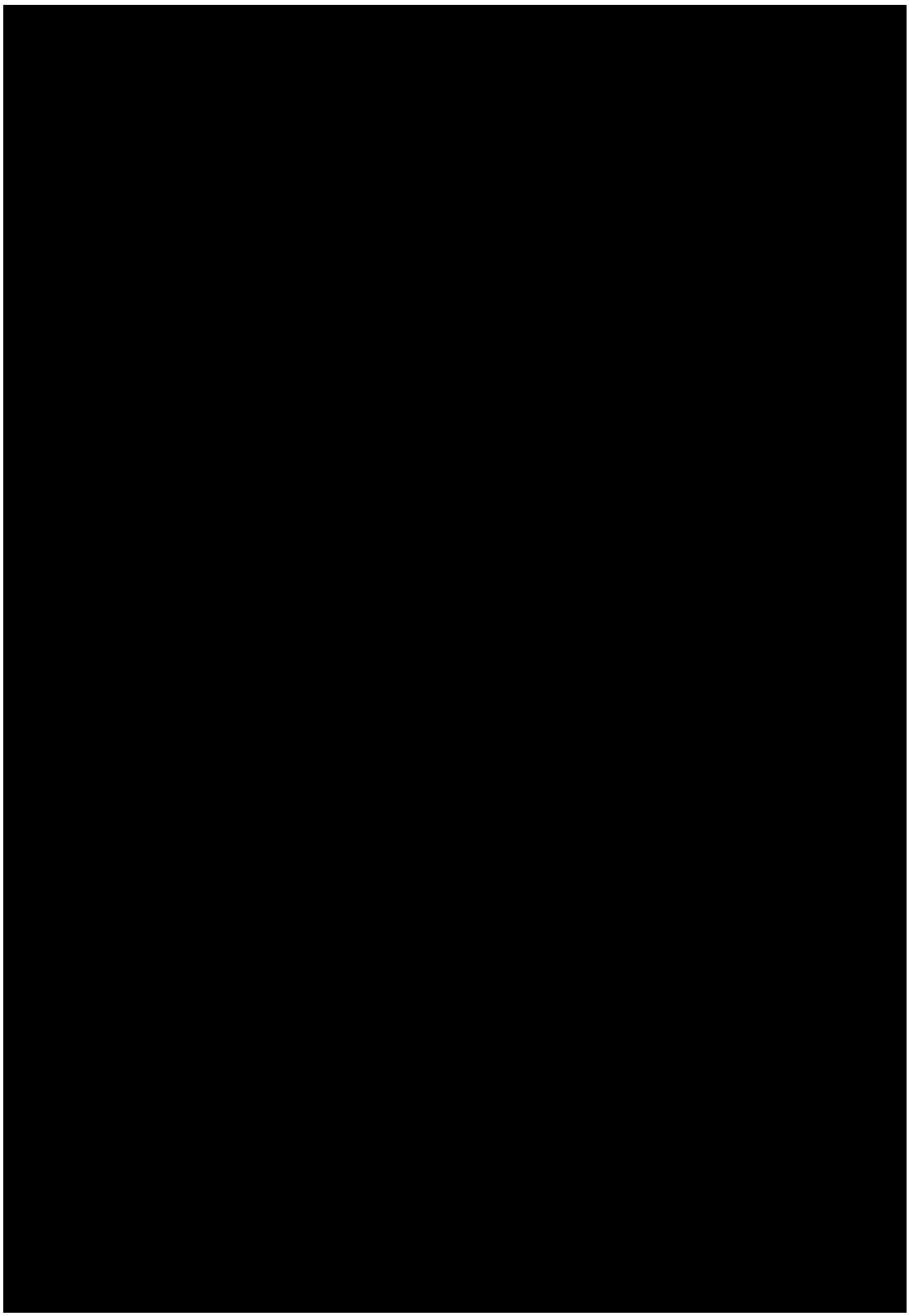


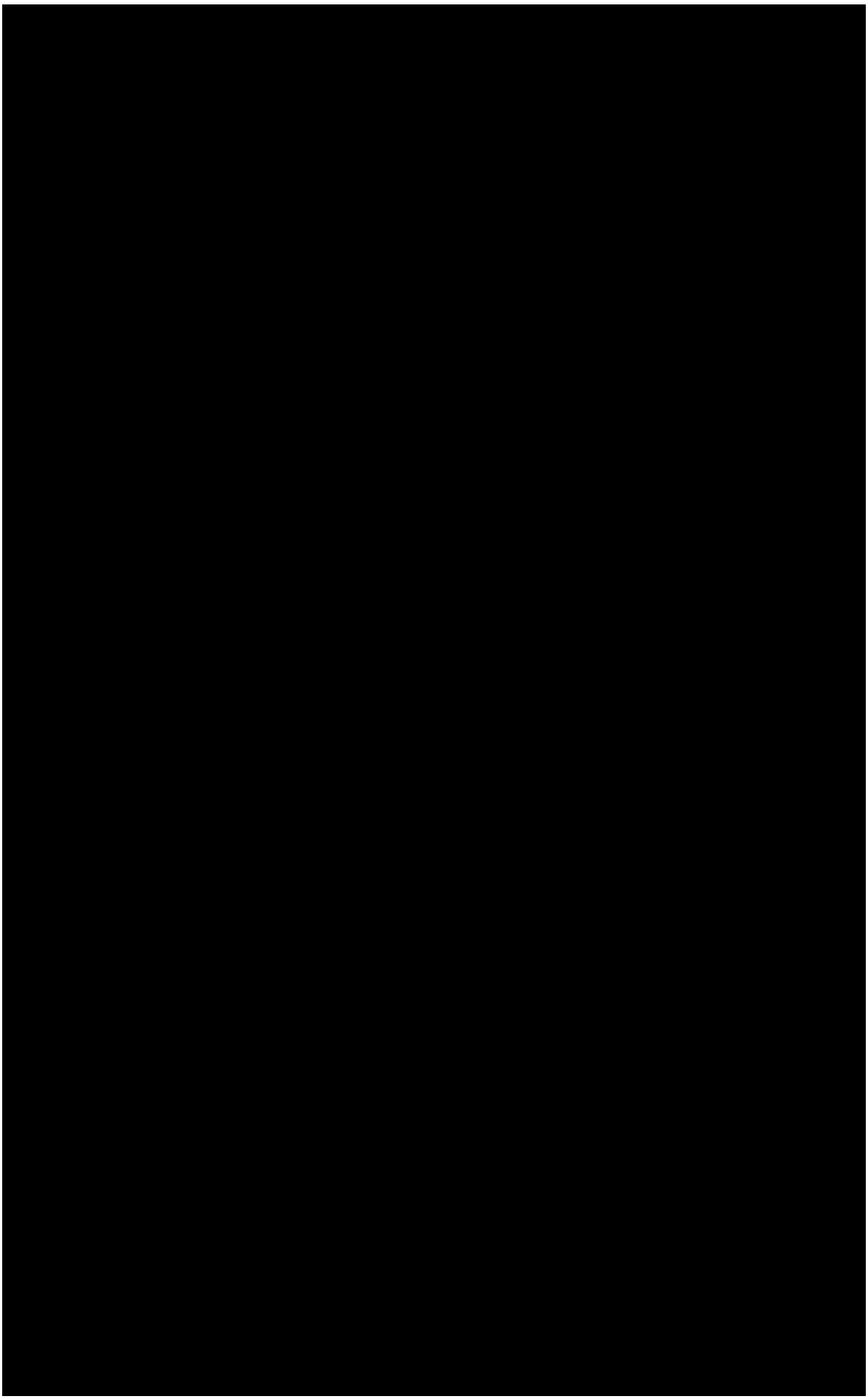


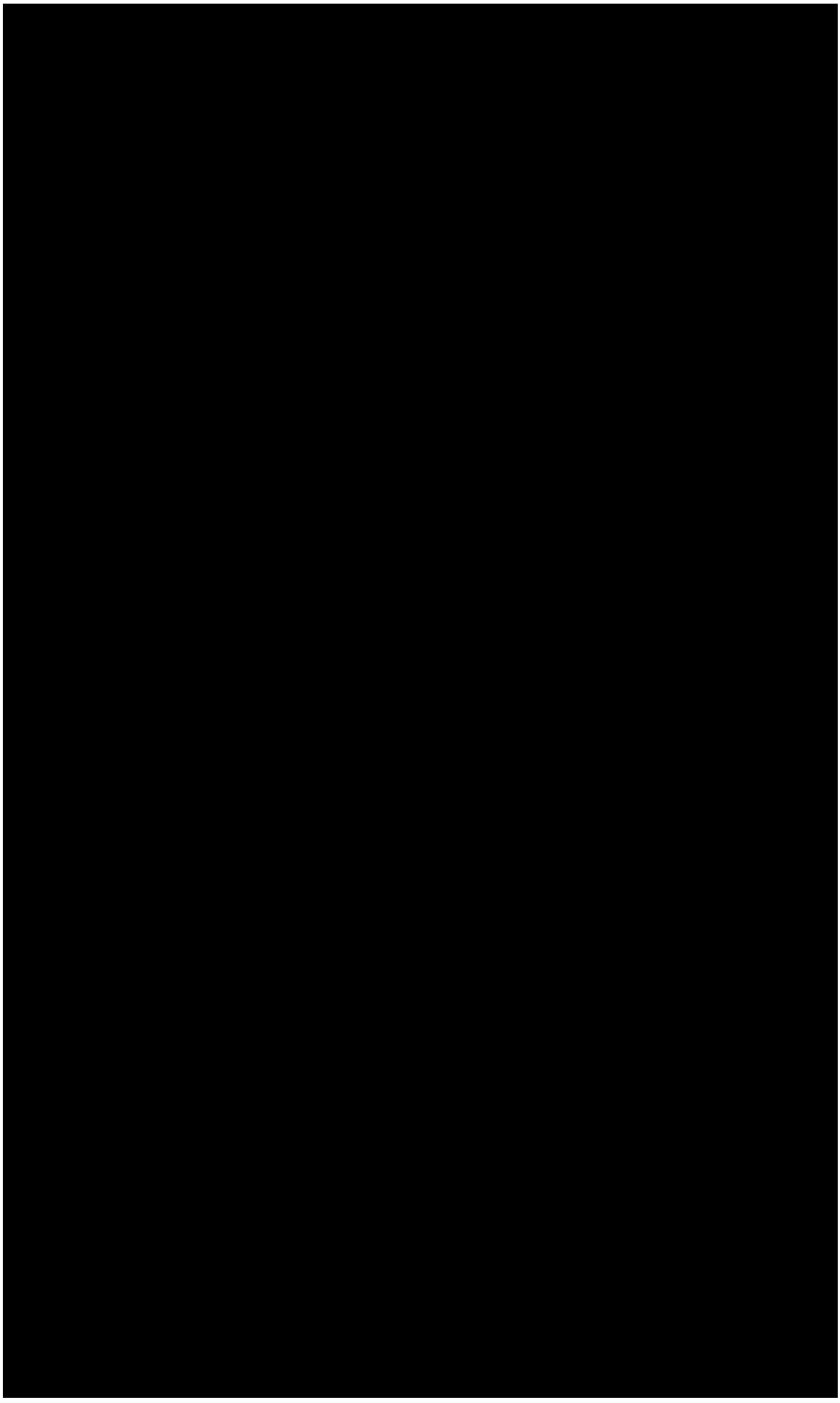


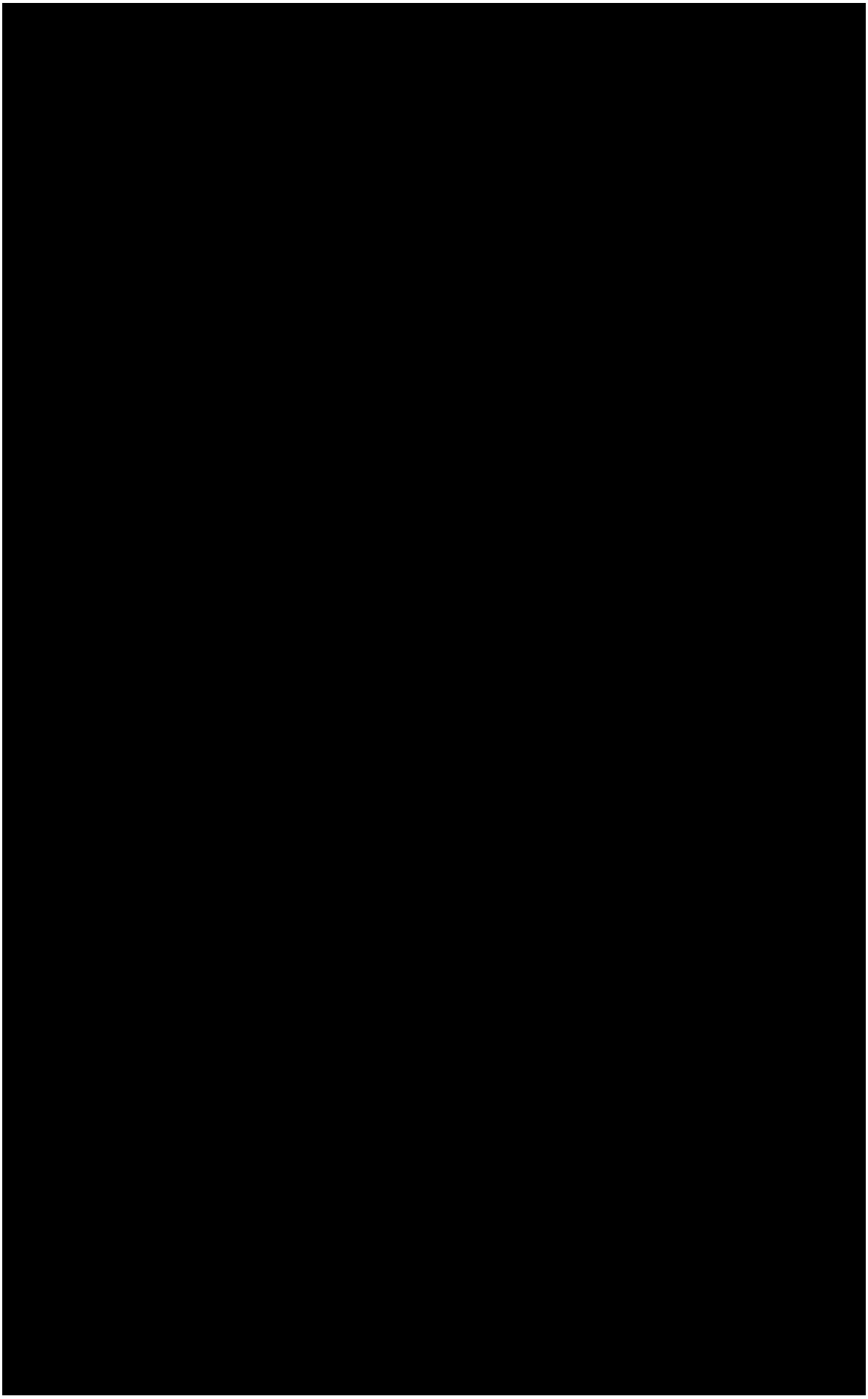


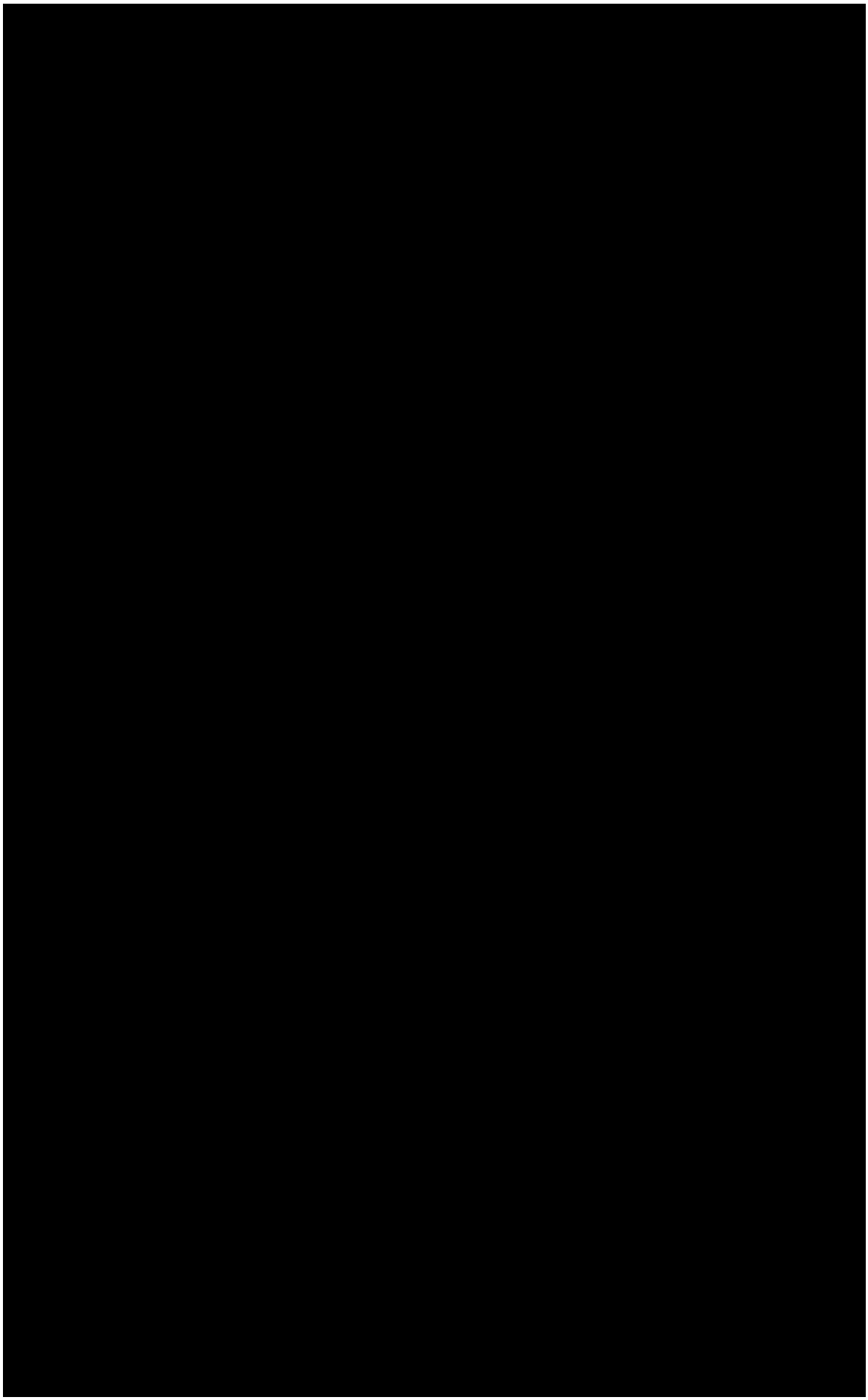
11.3 Transperineal Magnetic Resonance Imarge Targeted Biopsy versus Transperineal Template Prostate Mapping Biopsy in the Detection of Localised radiorecurrent Prostate Cancer

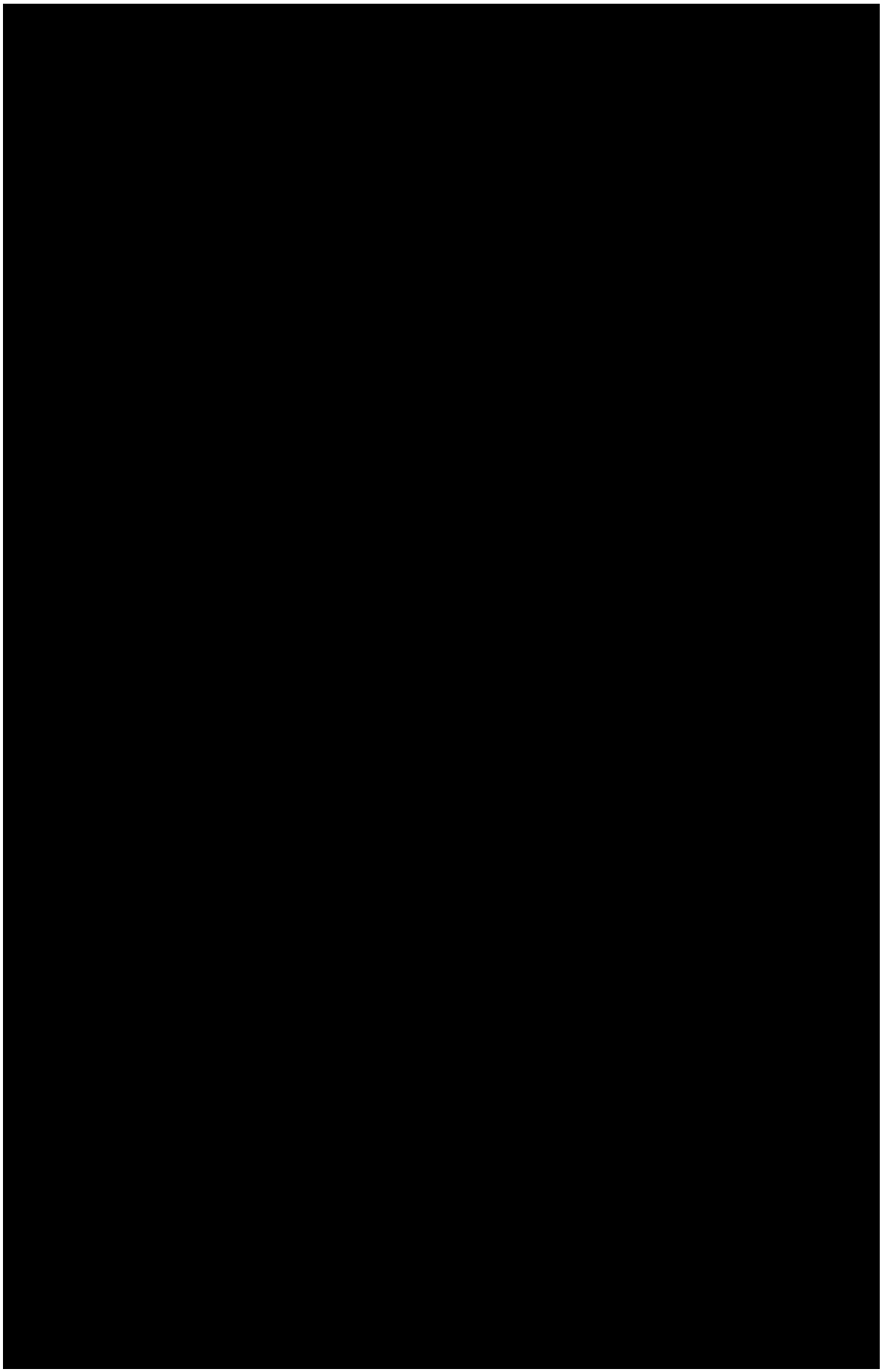


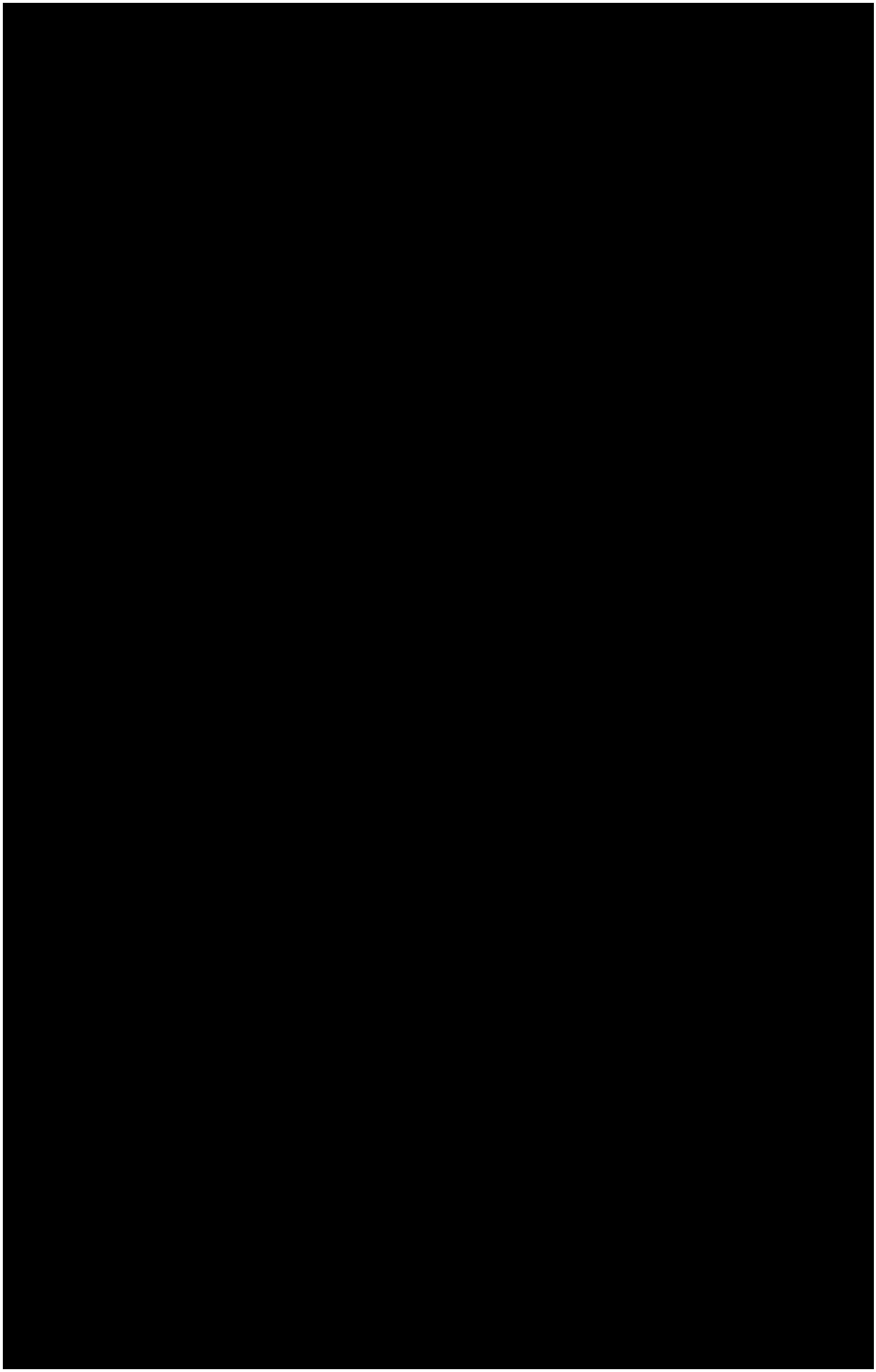


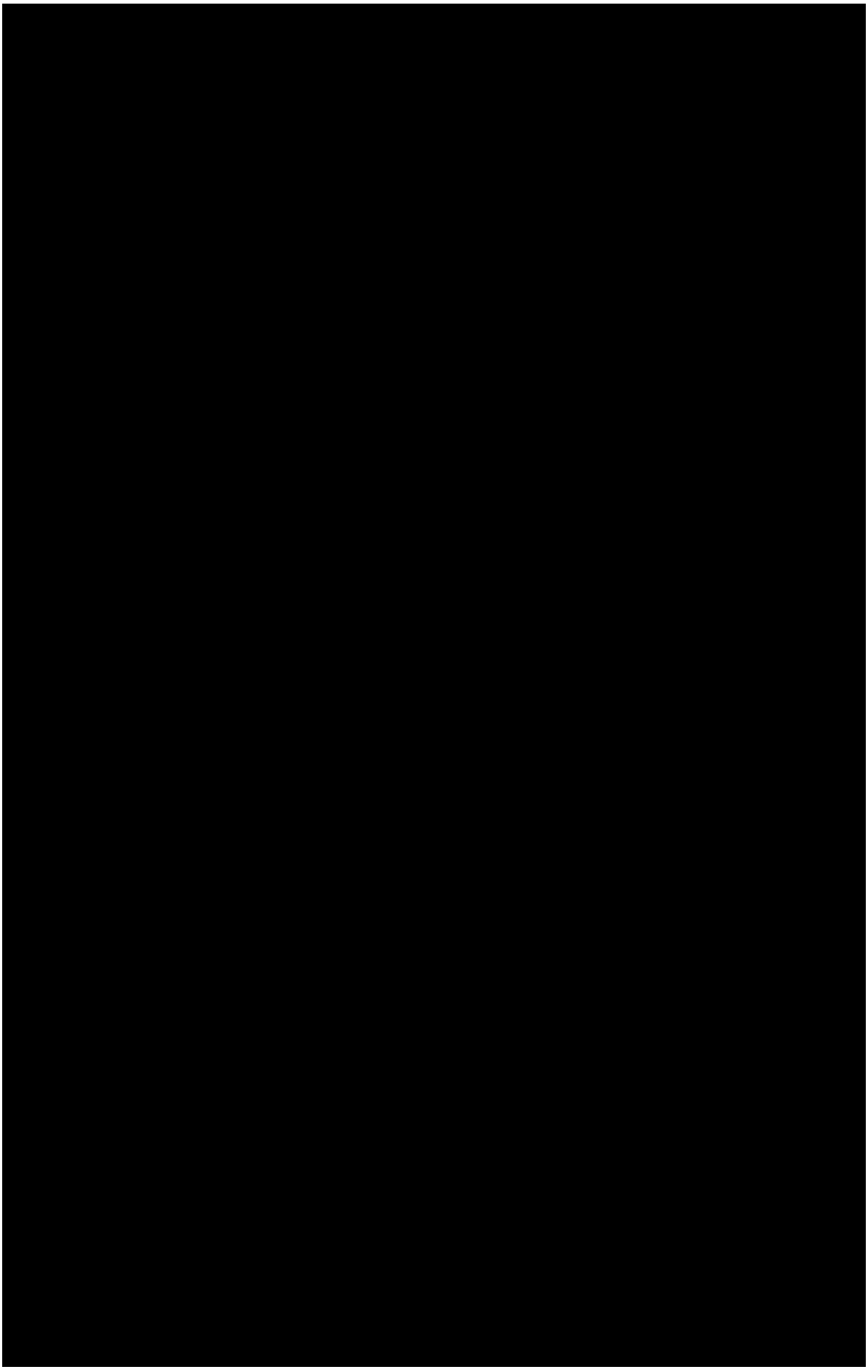




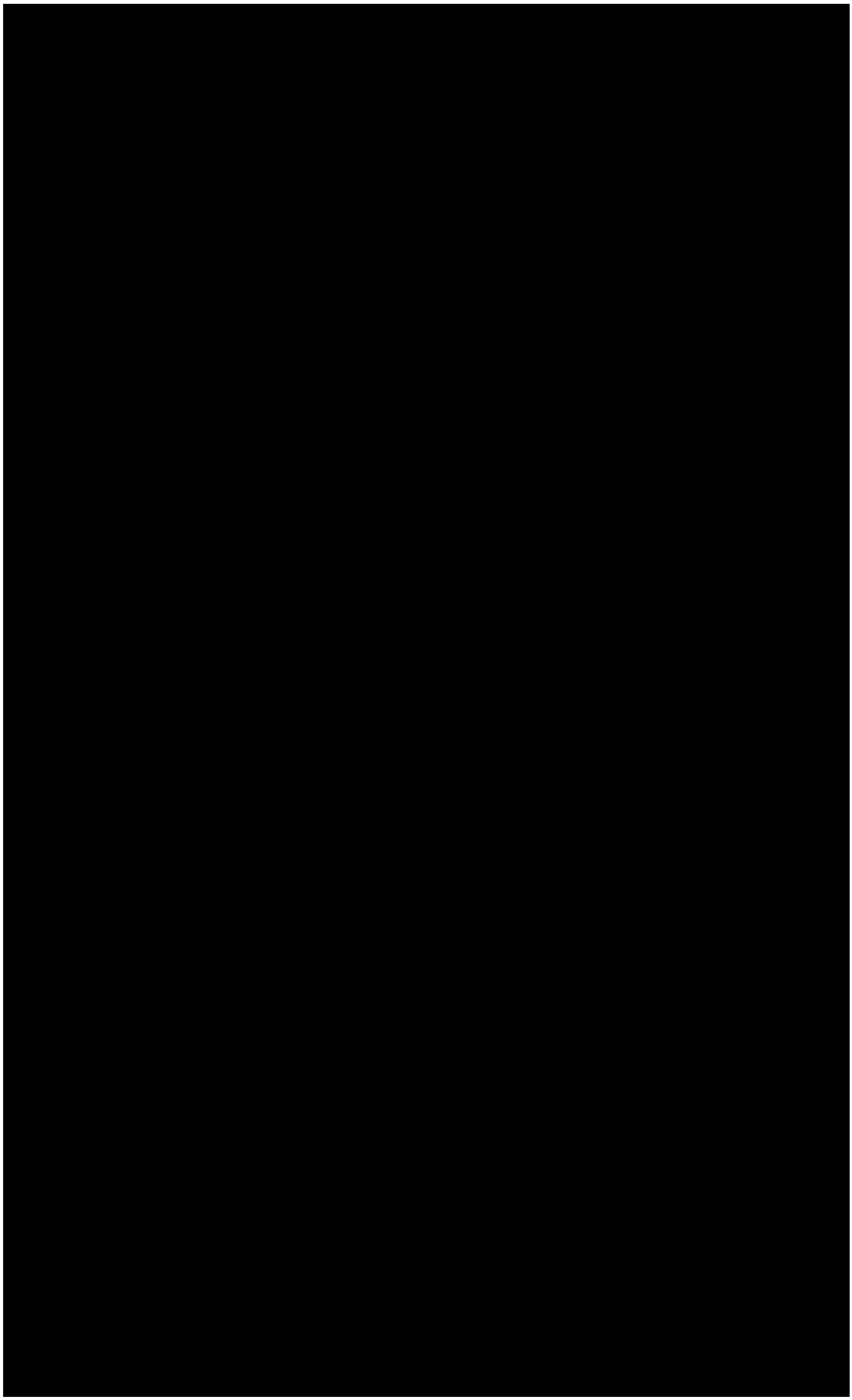


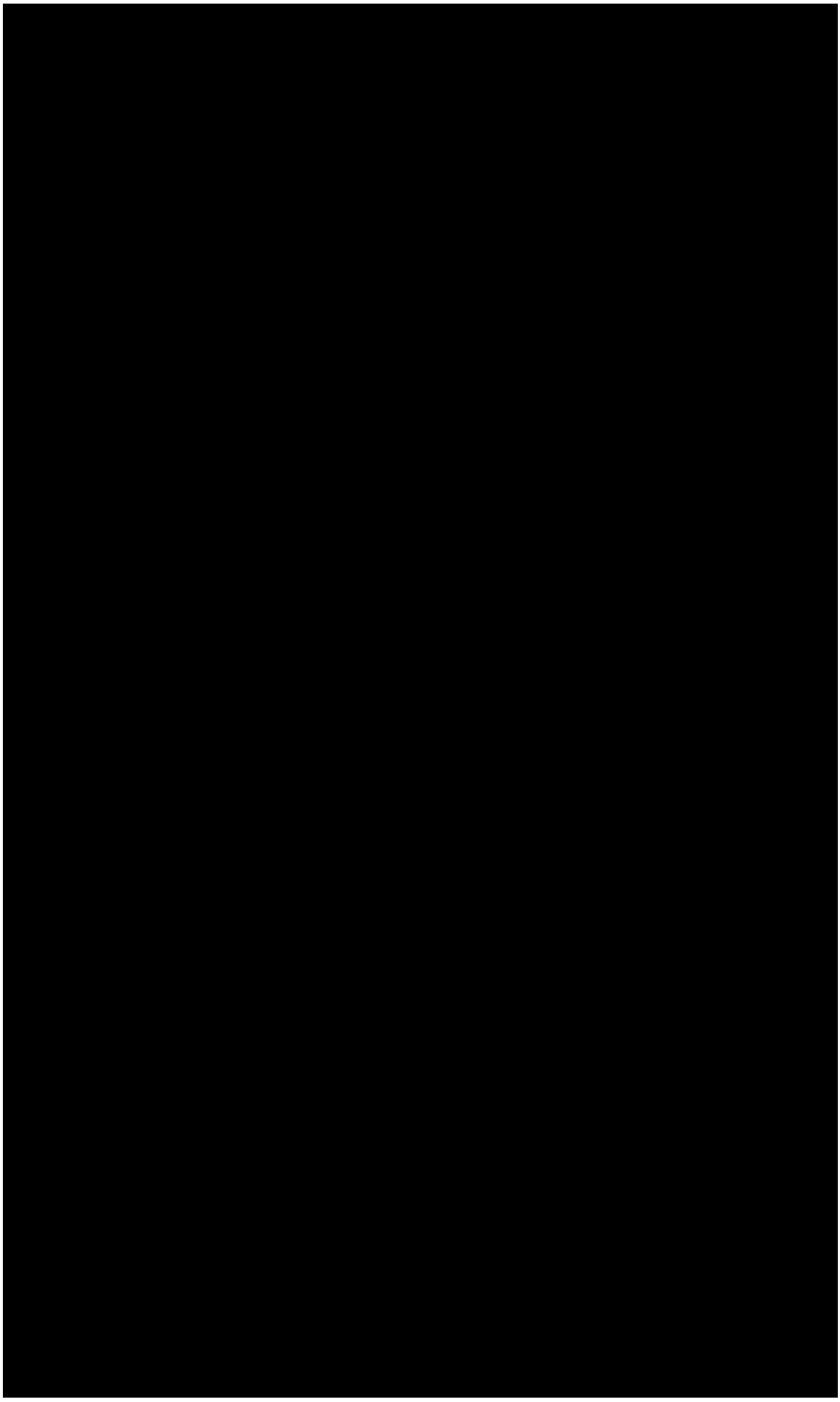


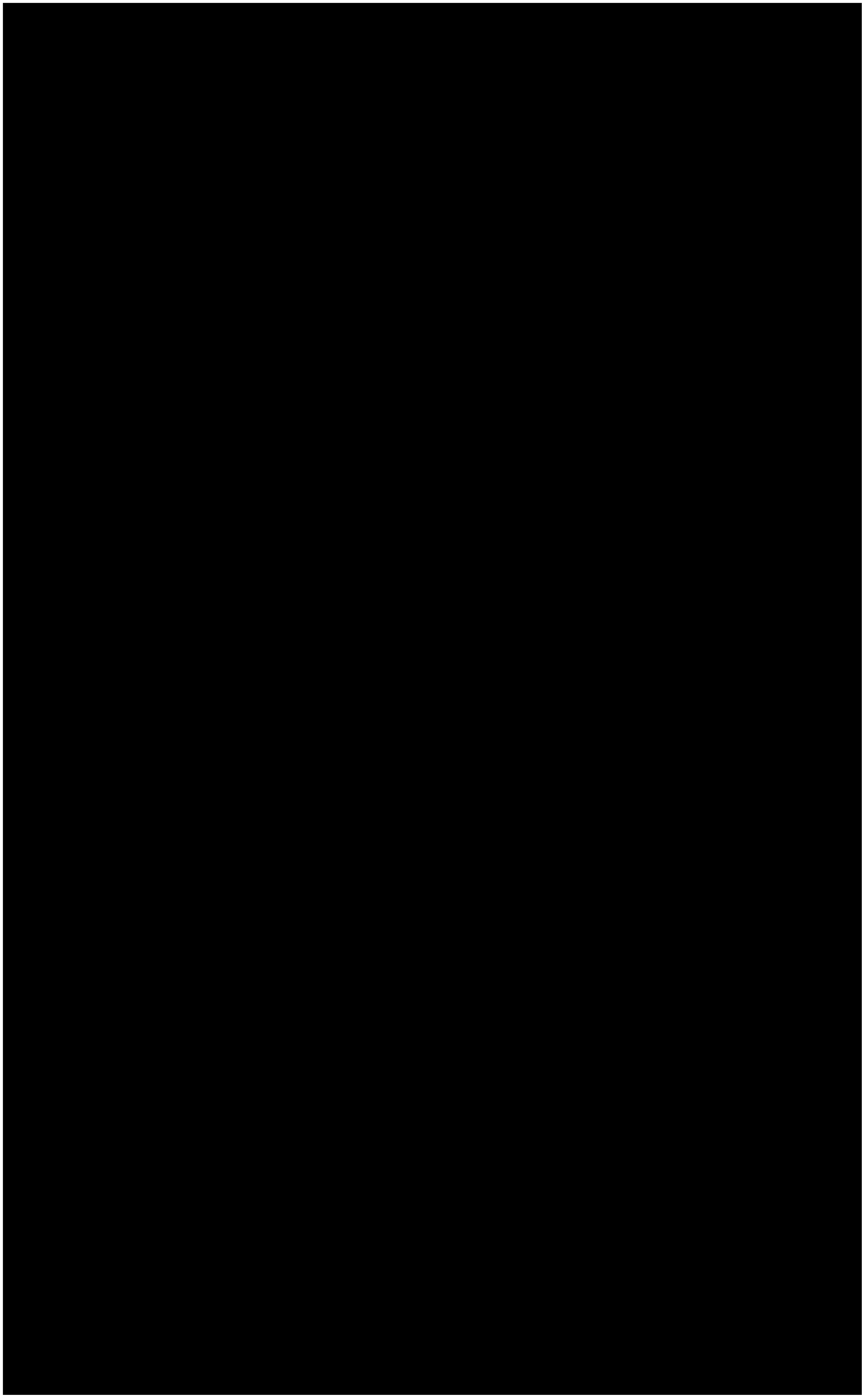


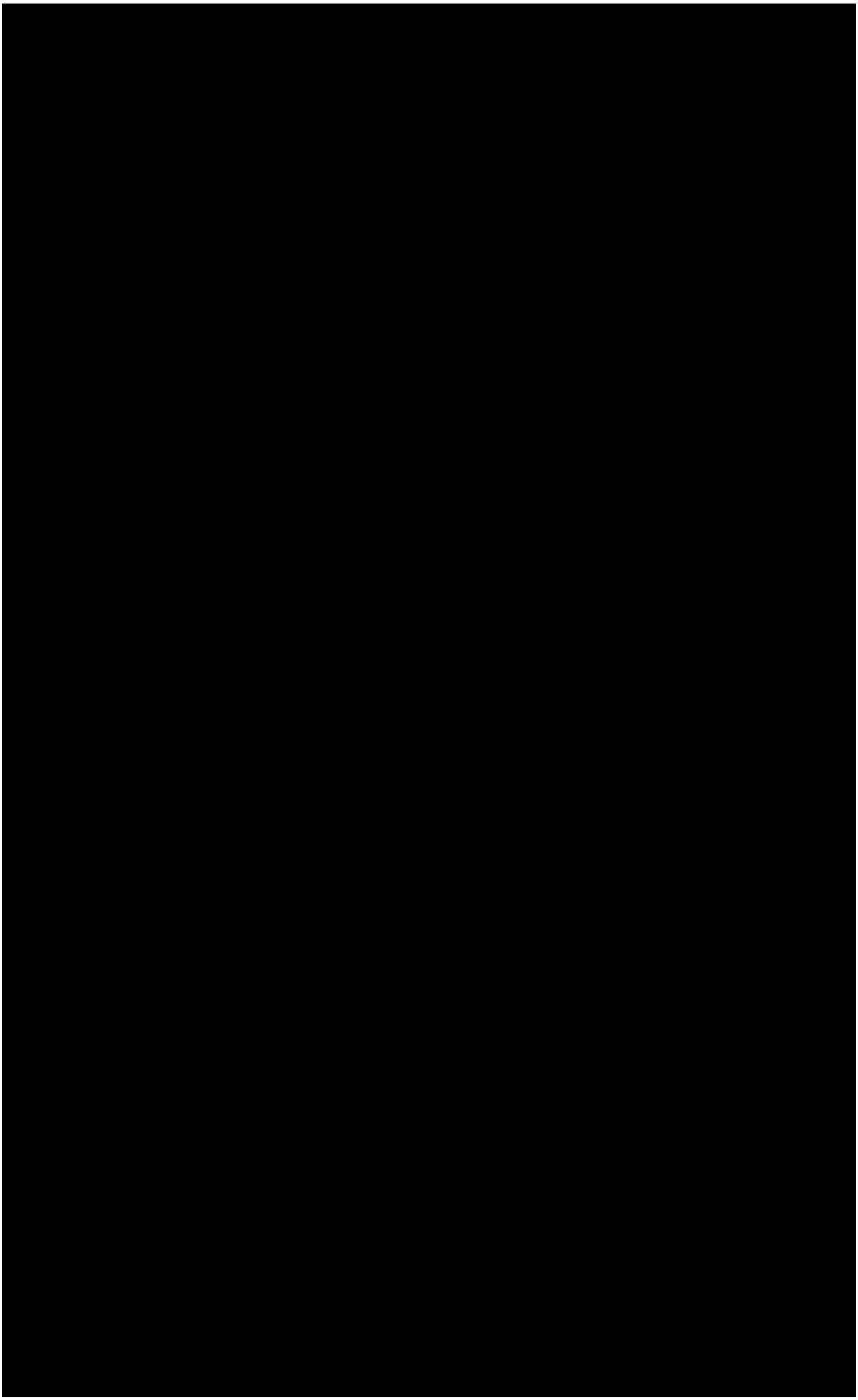


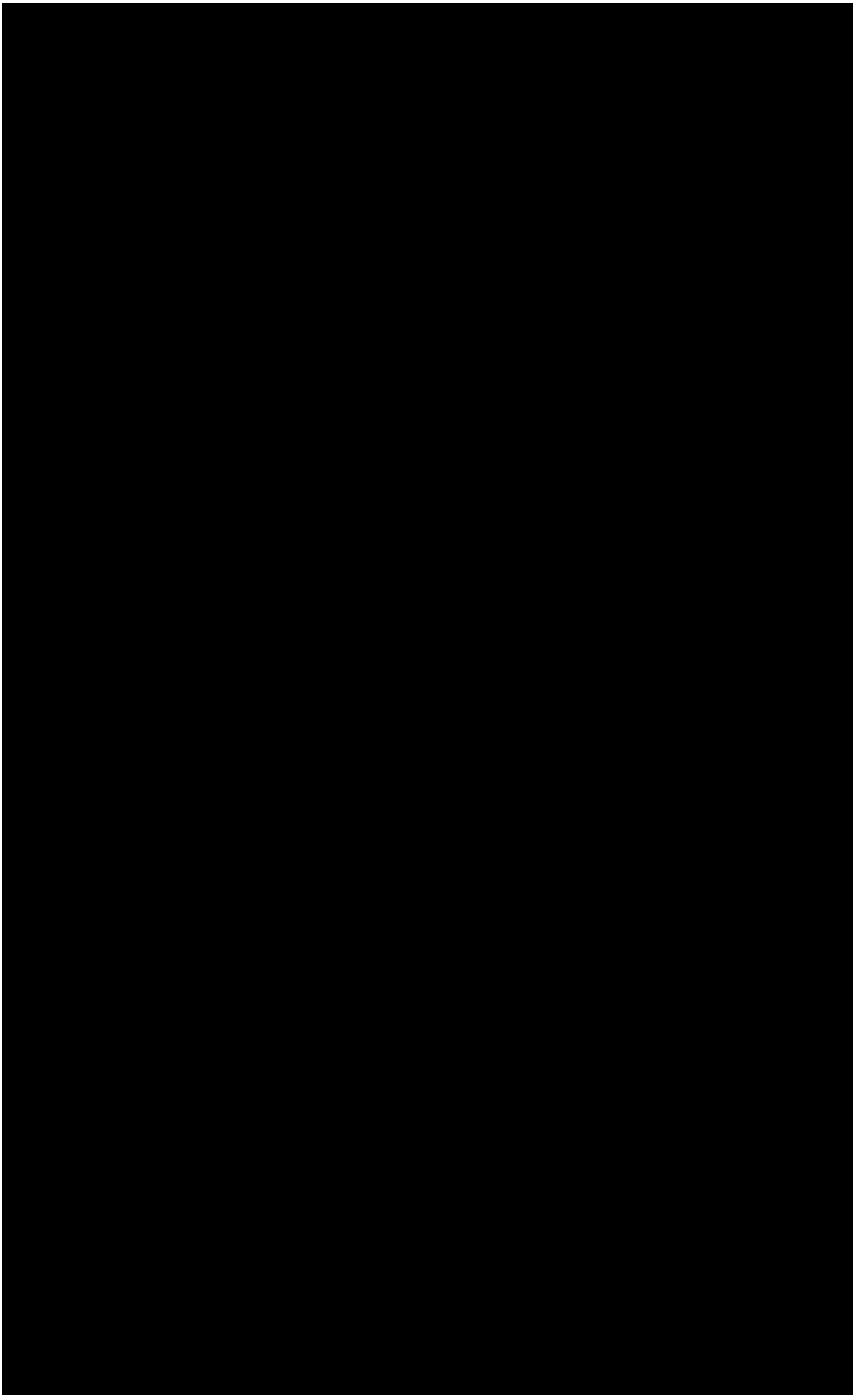
11.4 Focal Salvage high intensity focused ultrasound in radiorecurrent prostate cancer

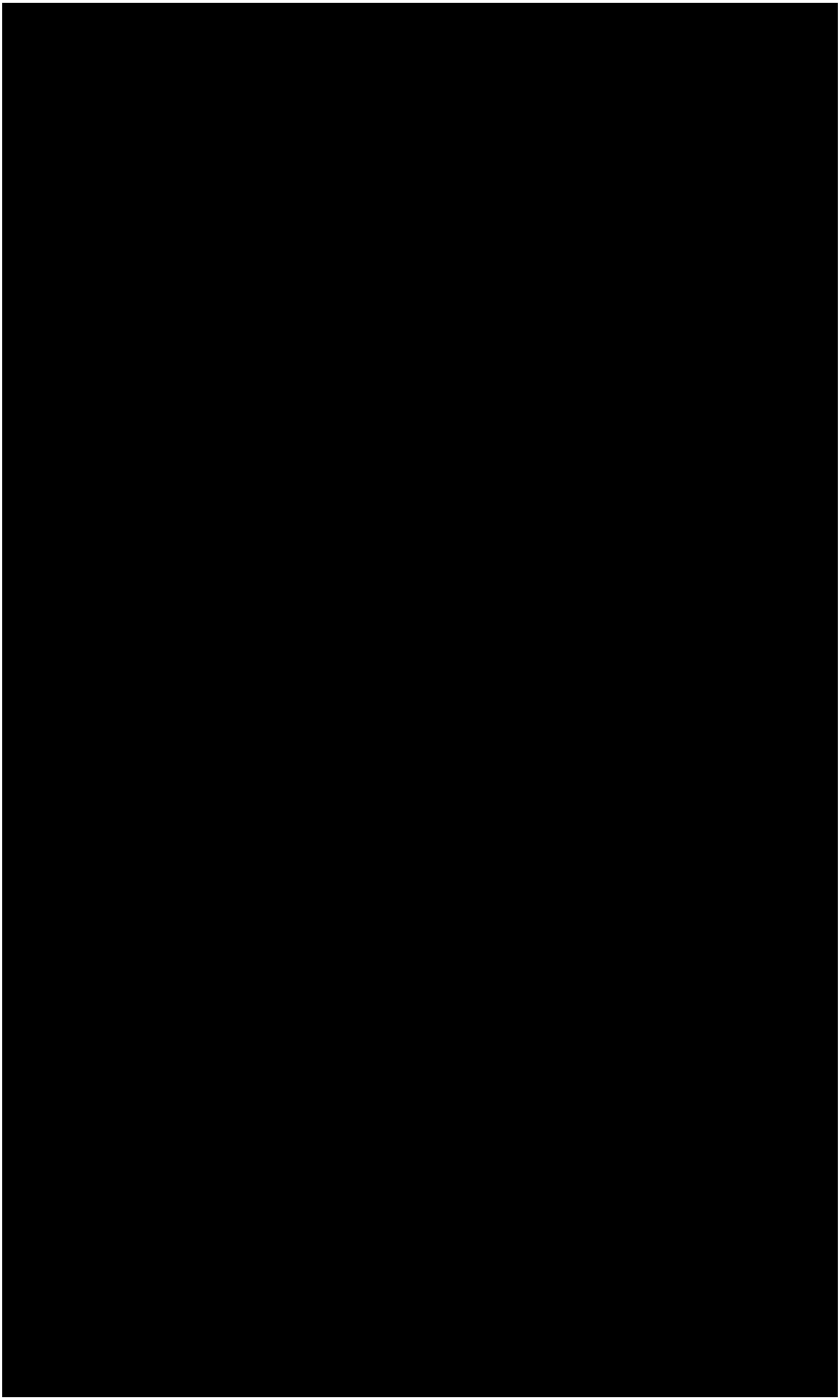


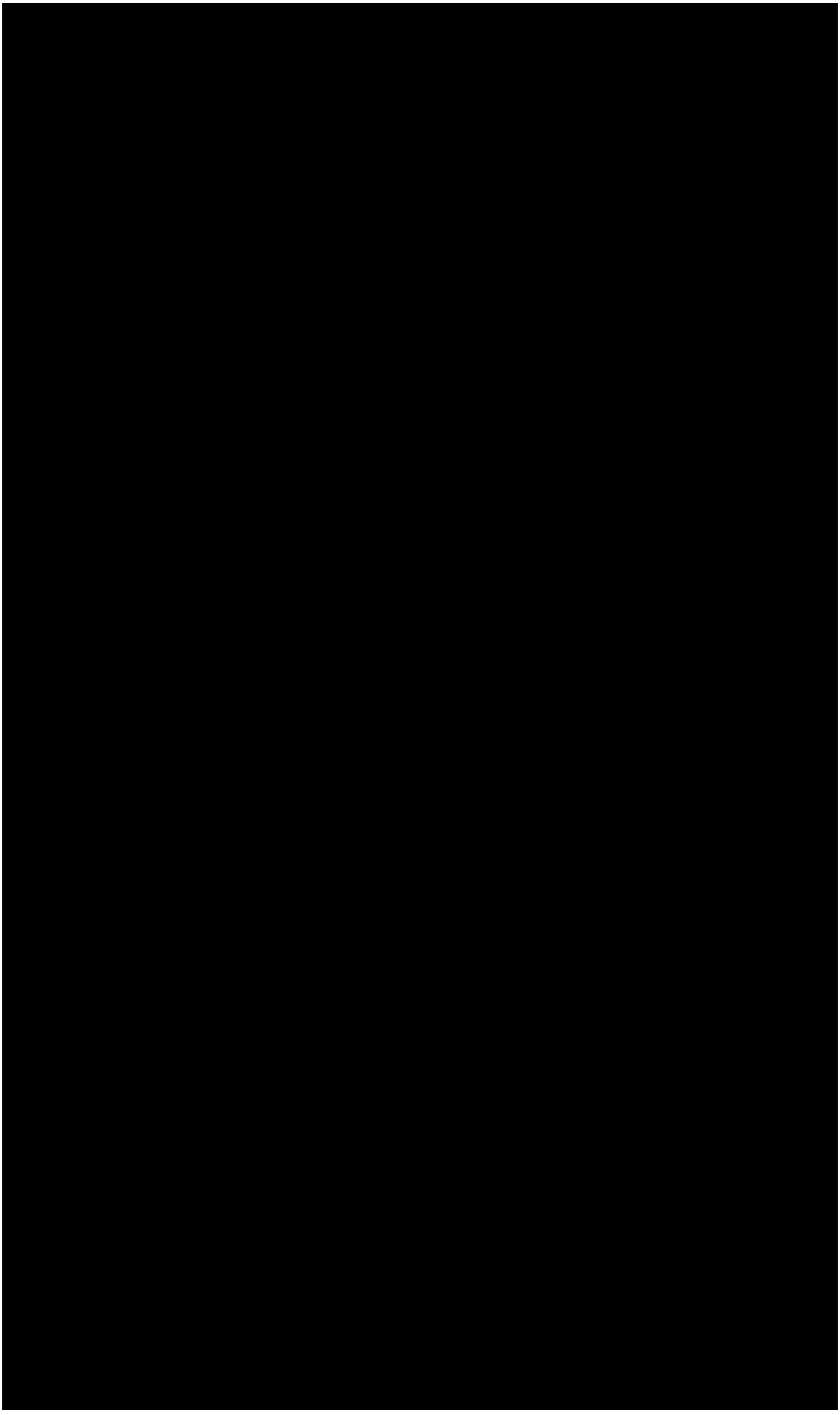


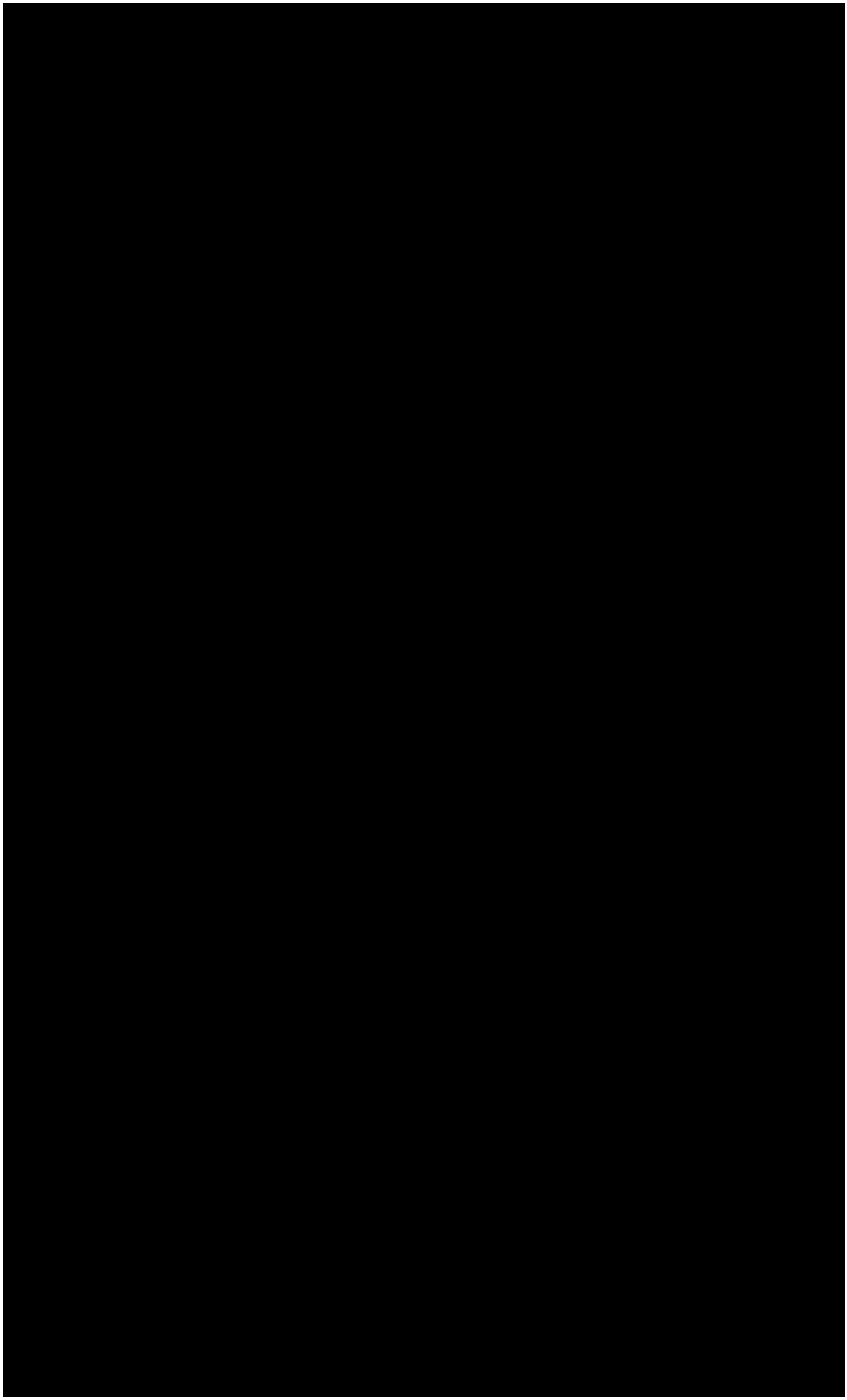


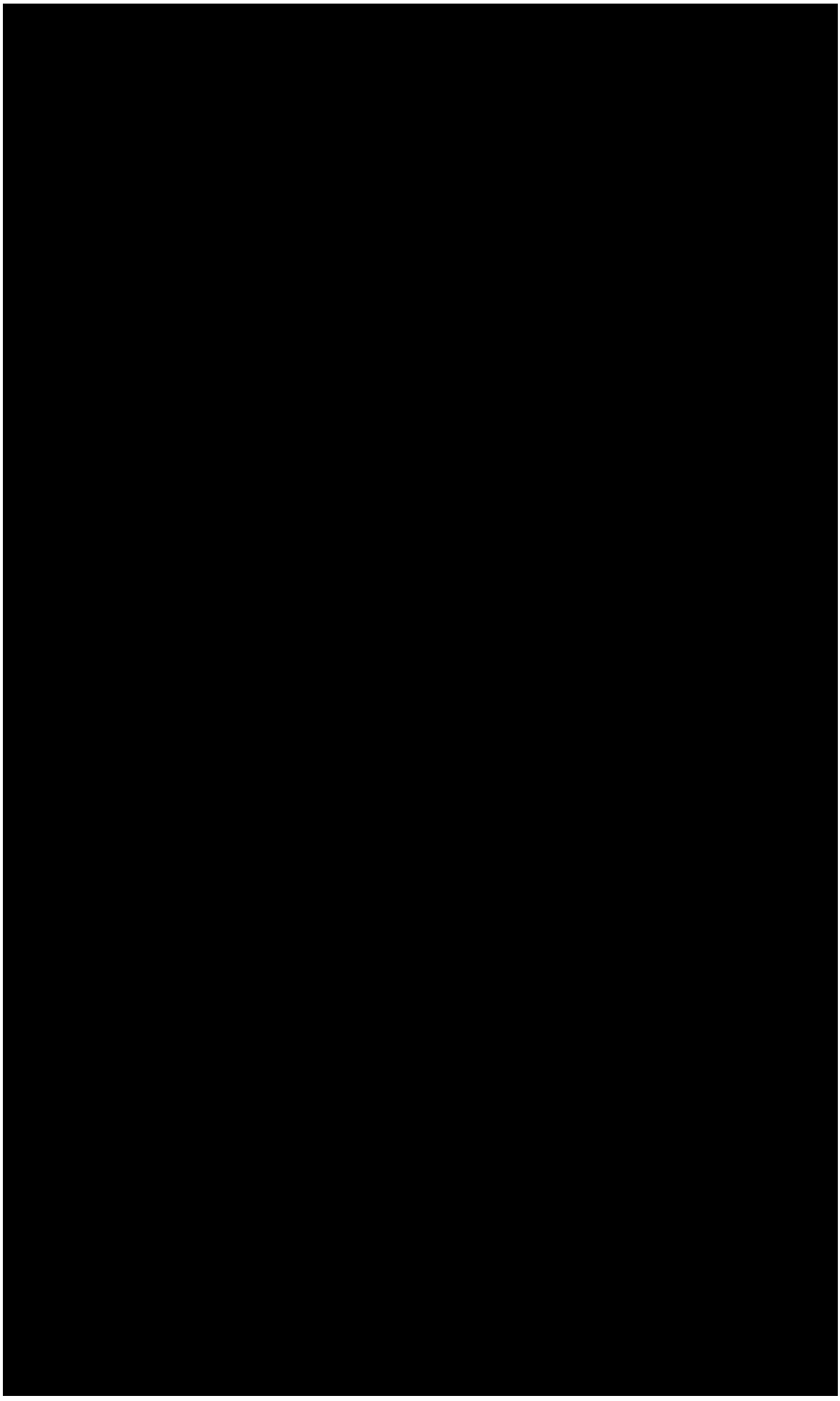


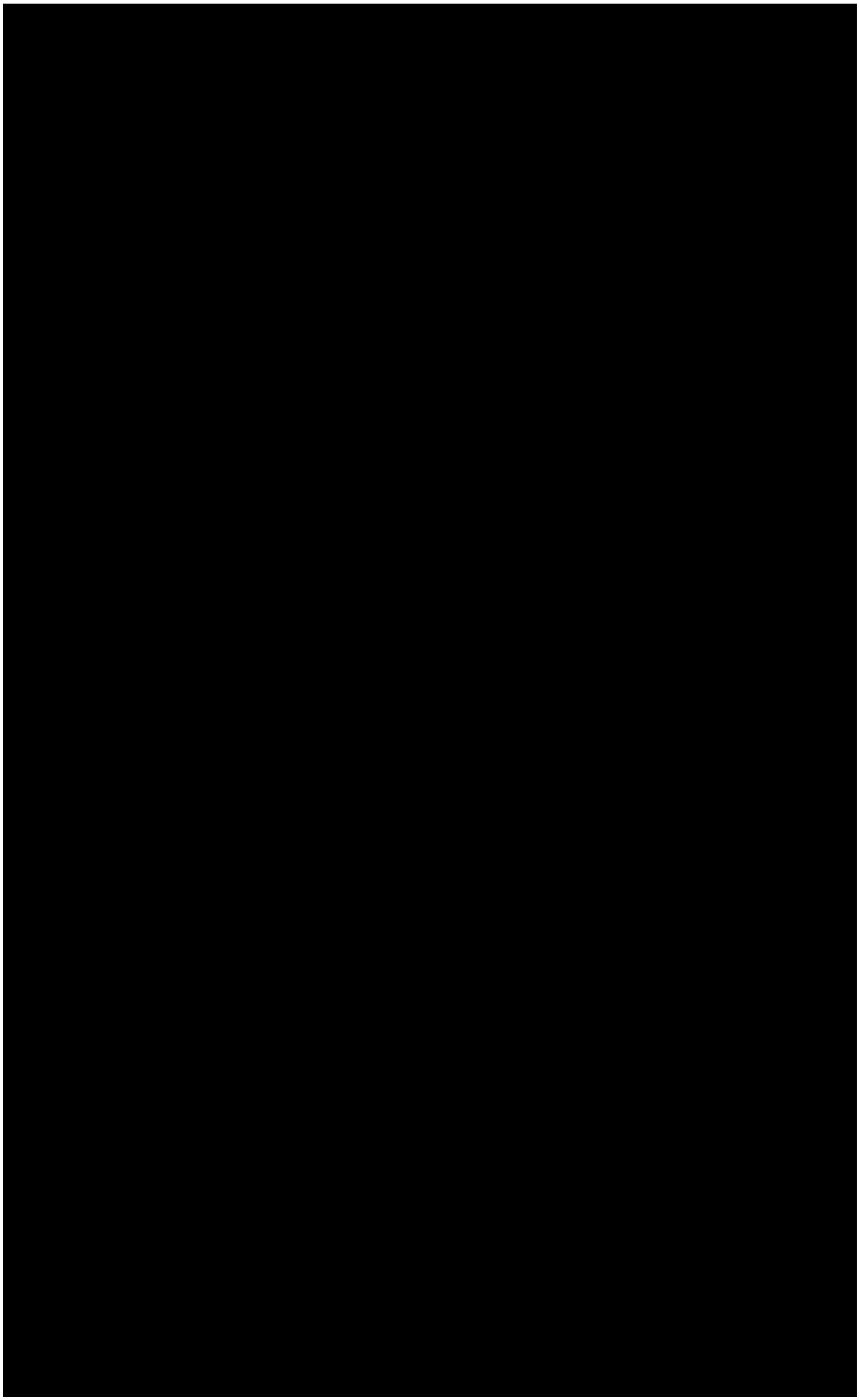


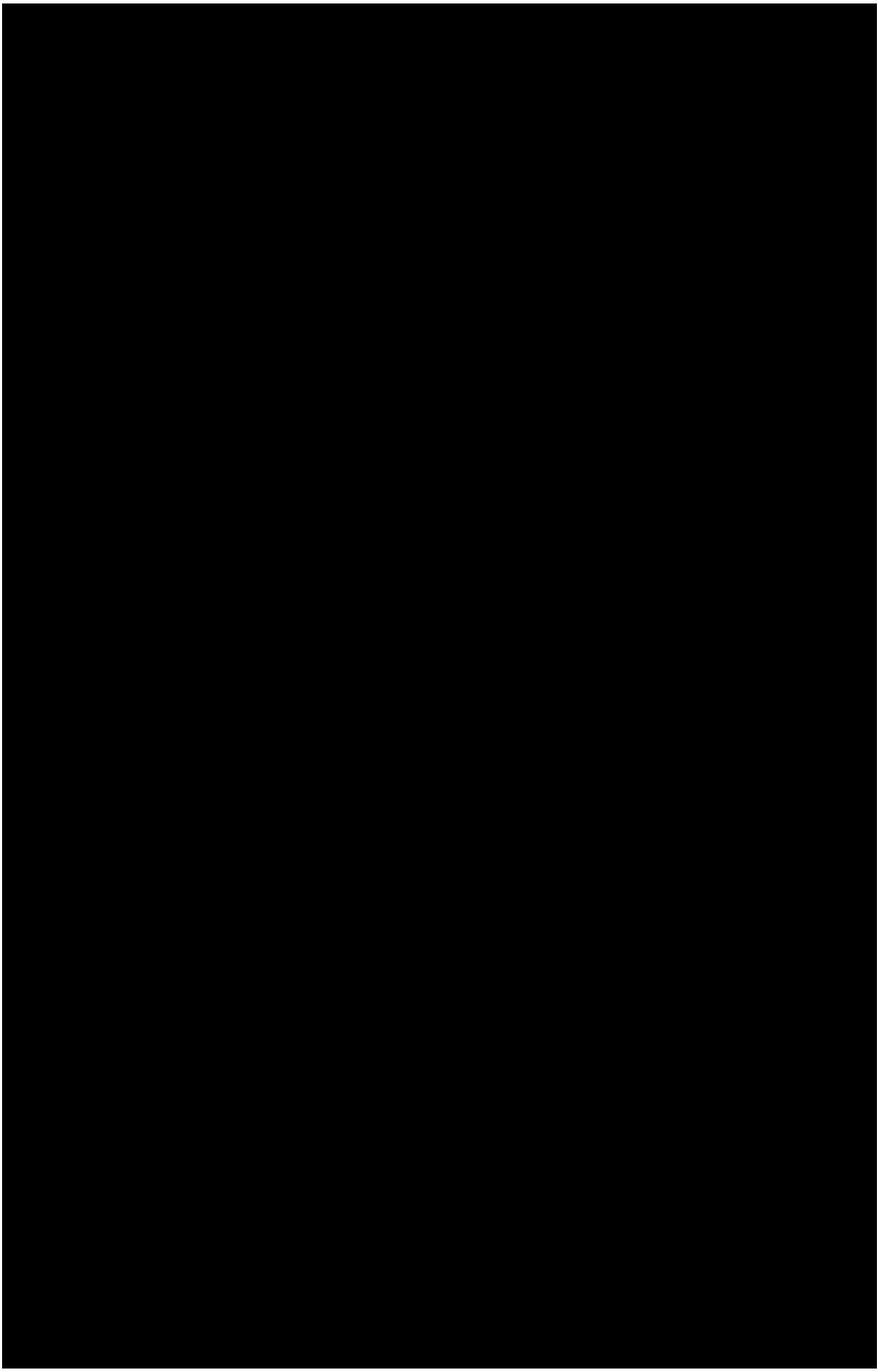


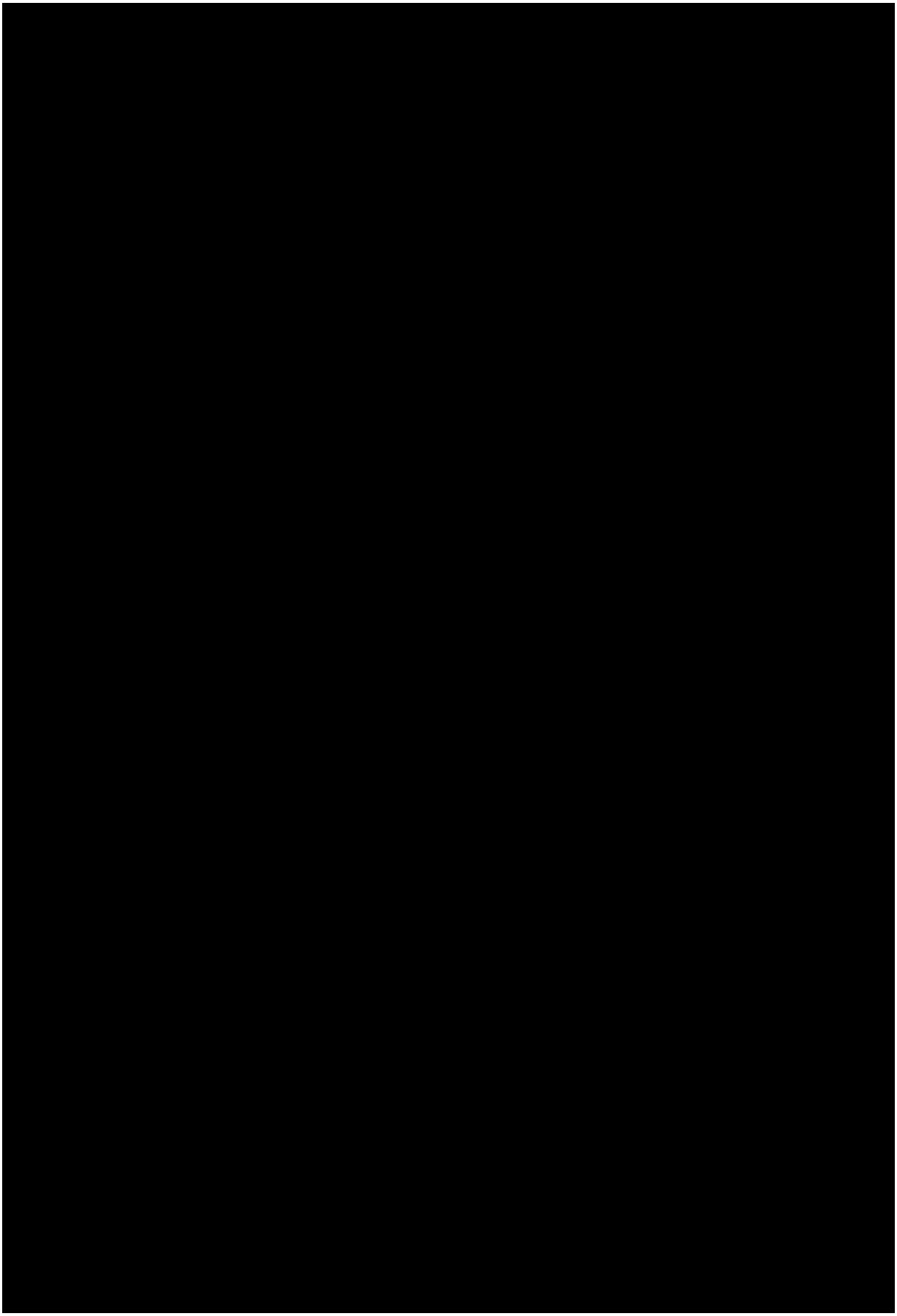


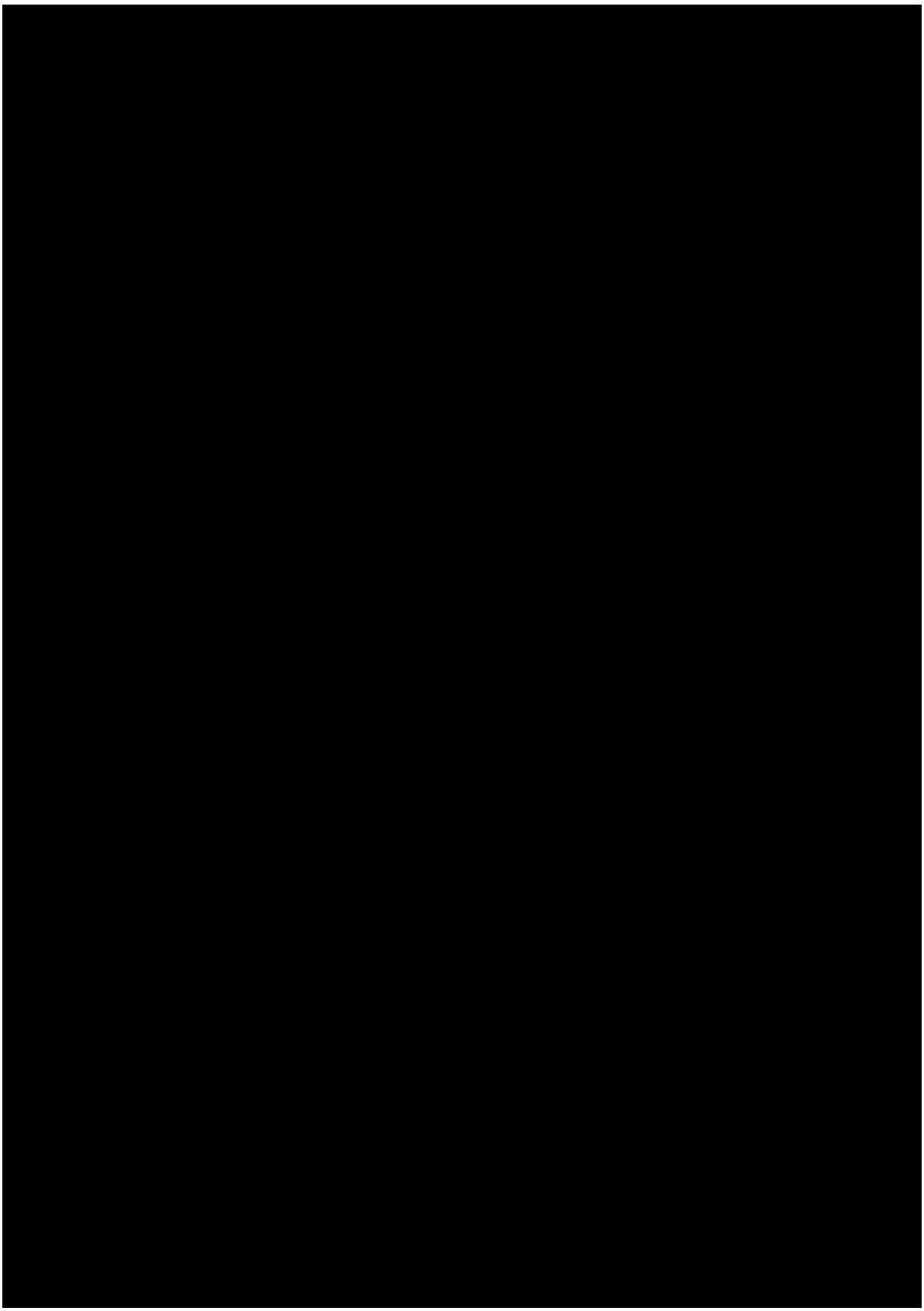


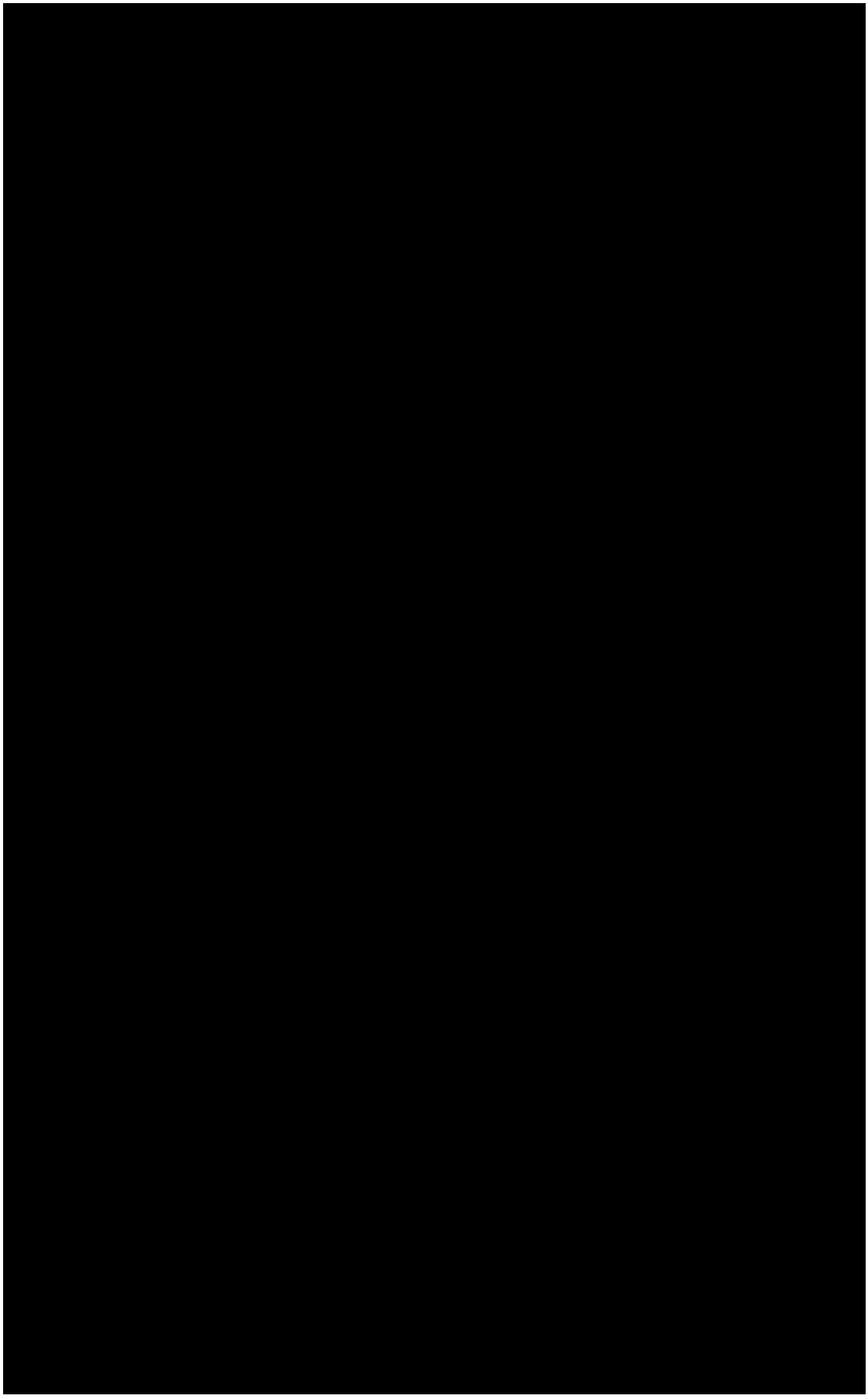


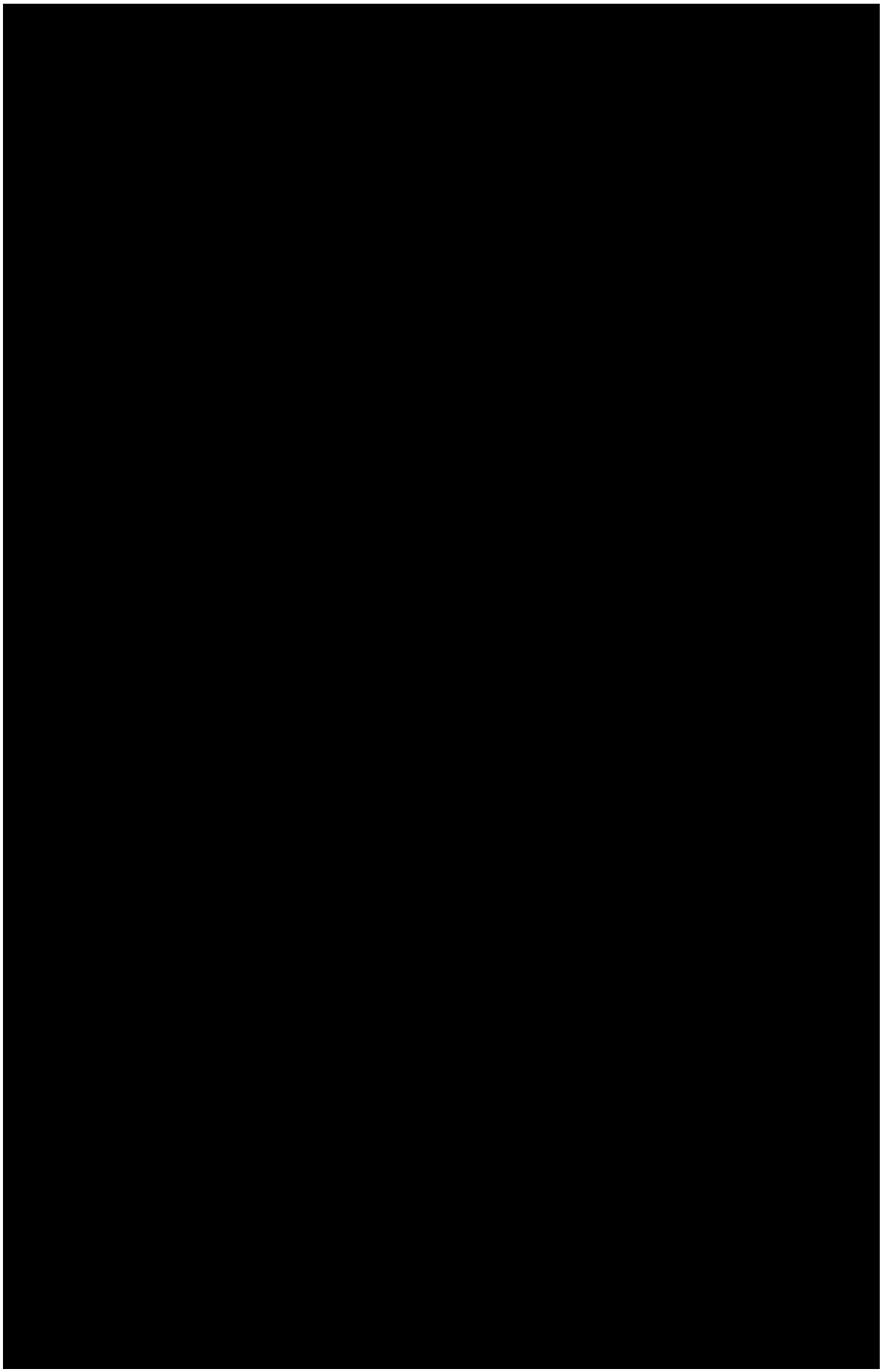


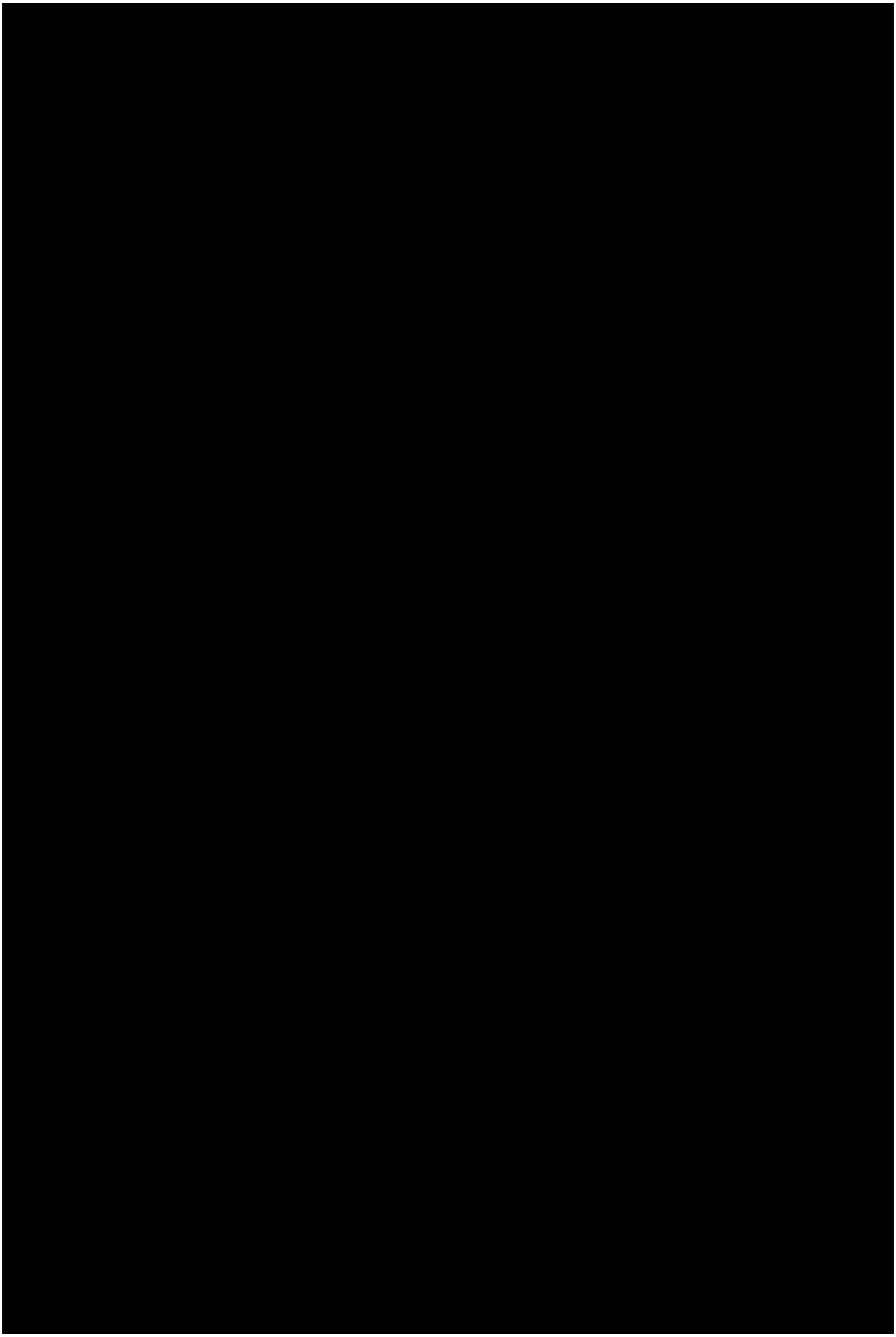


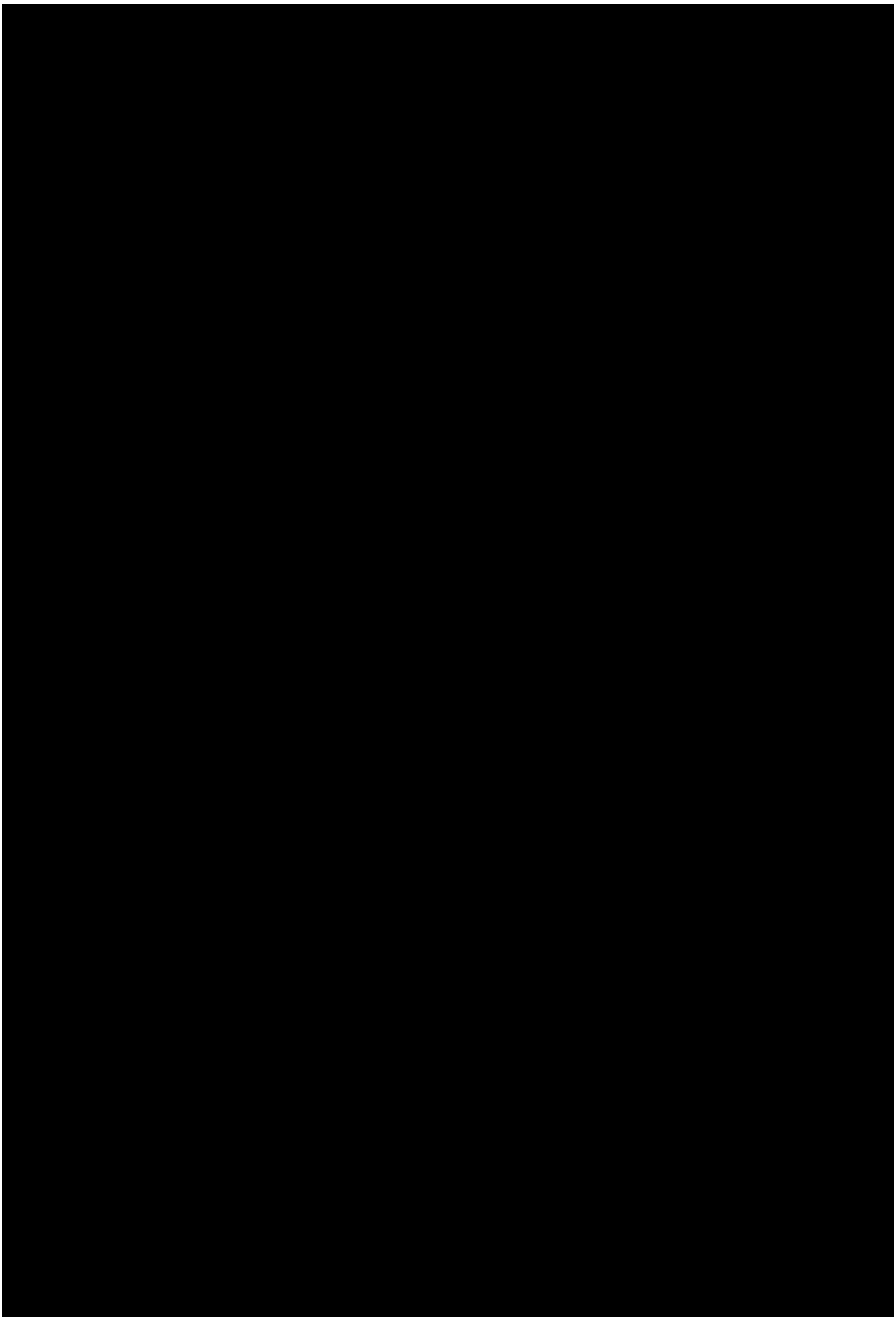


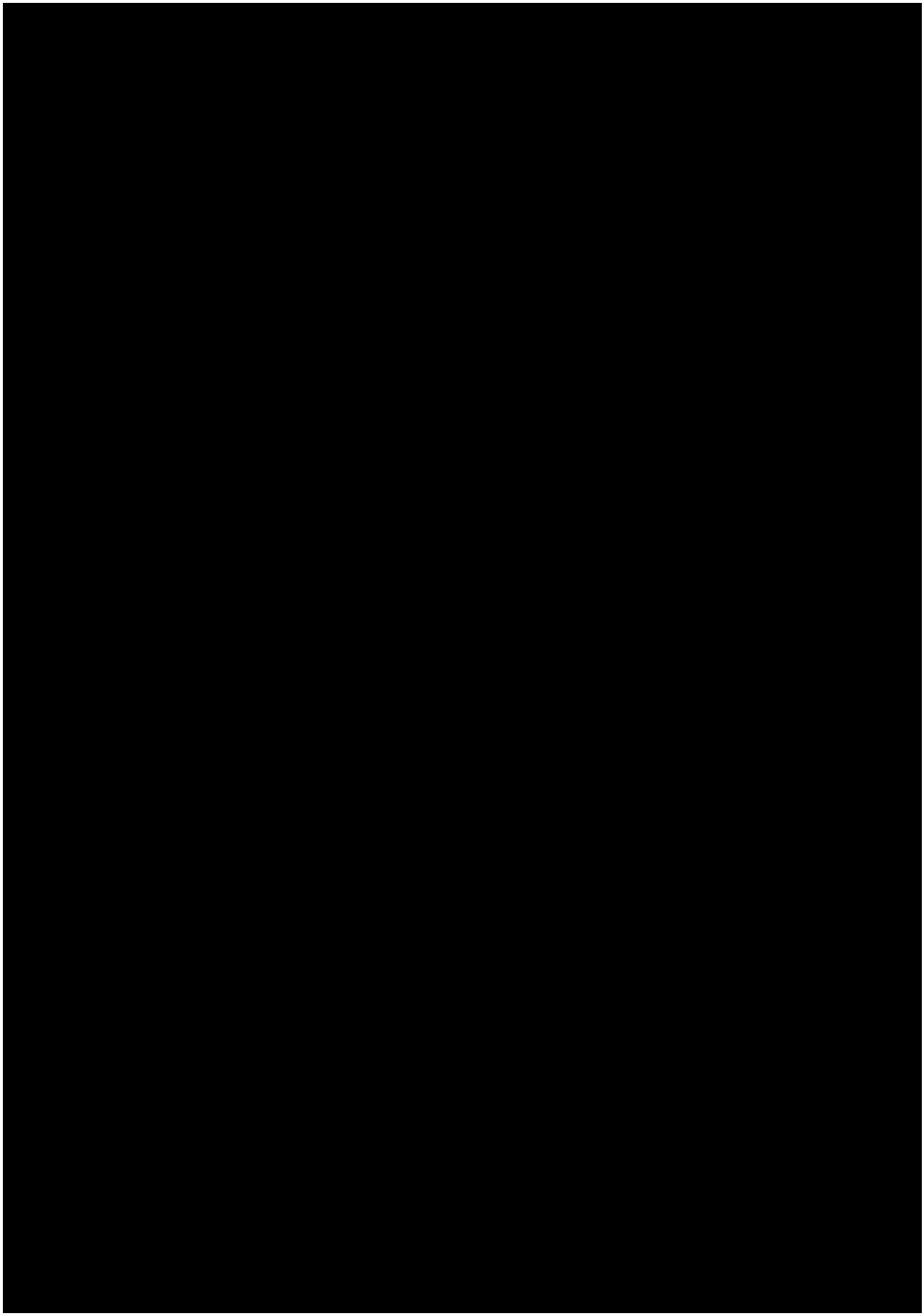


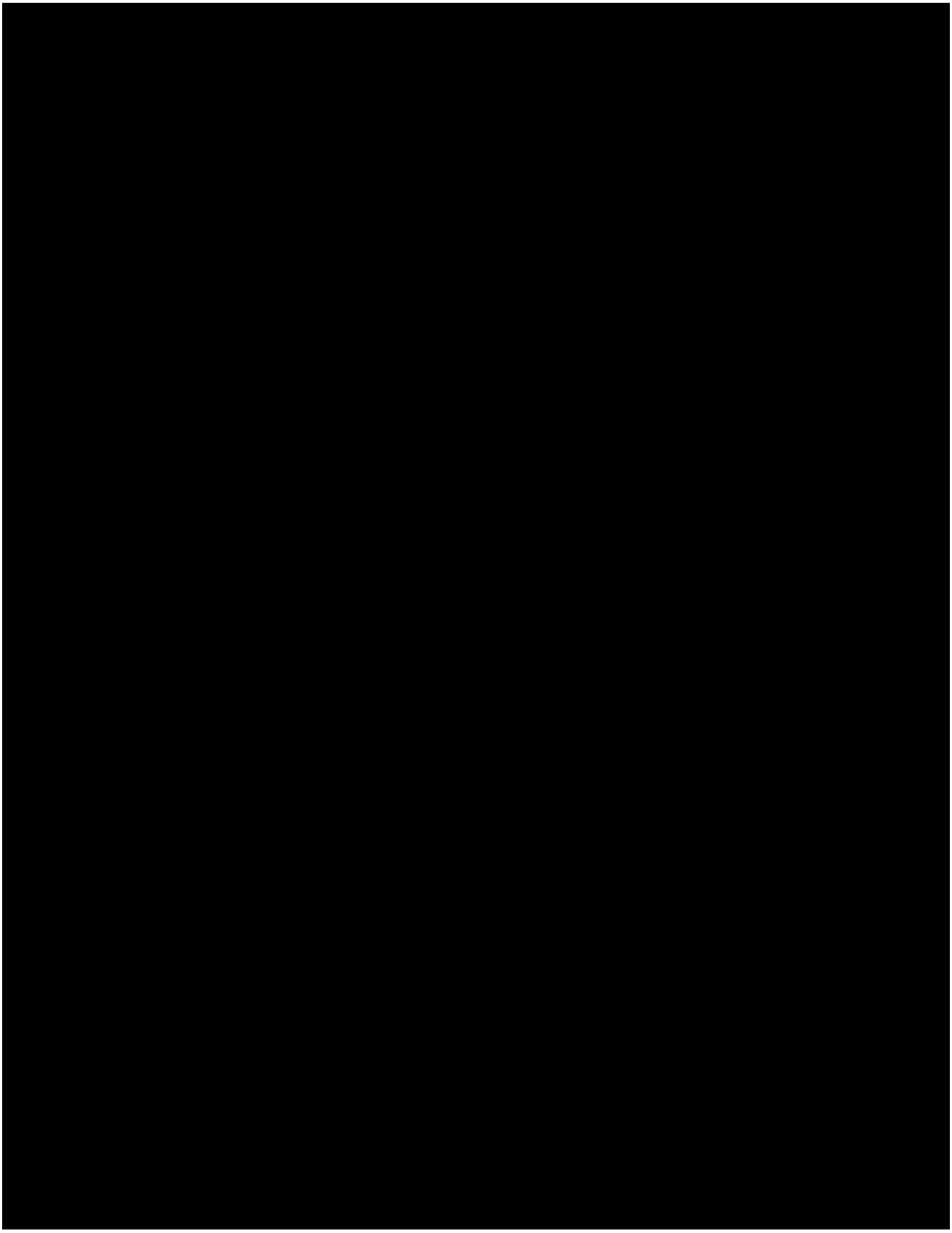


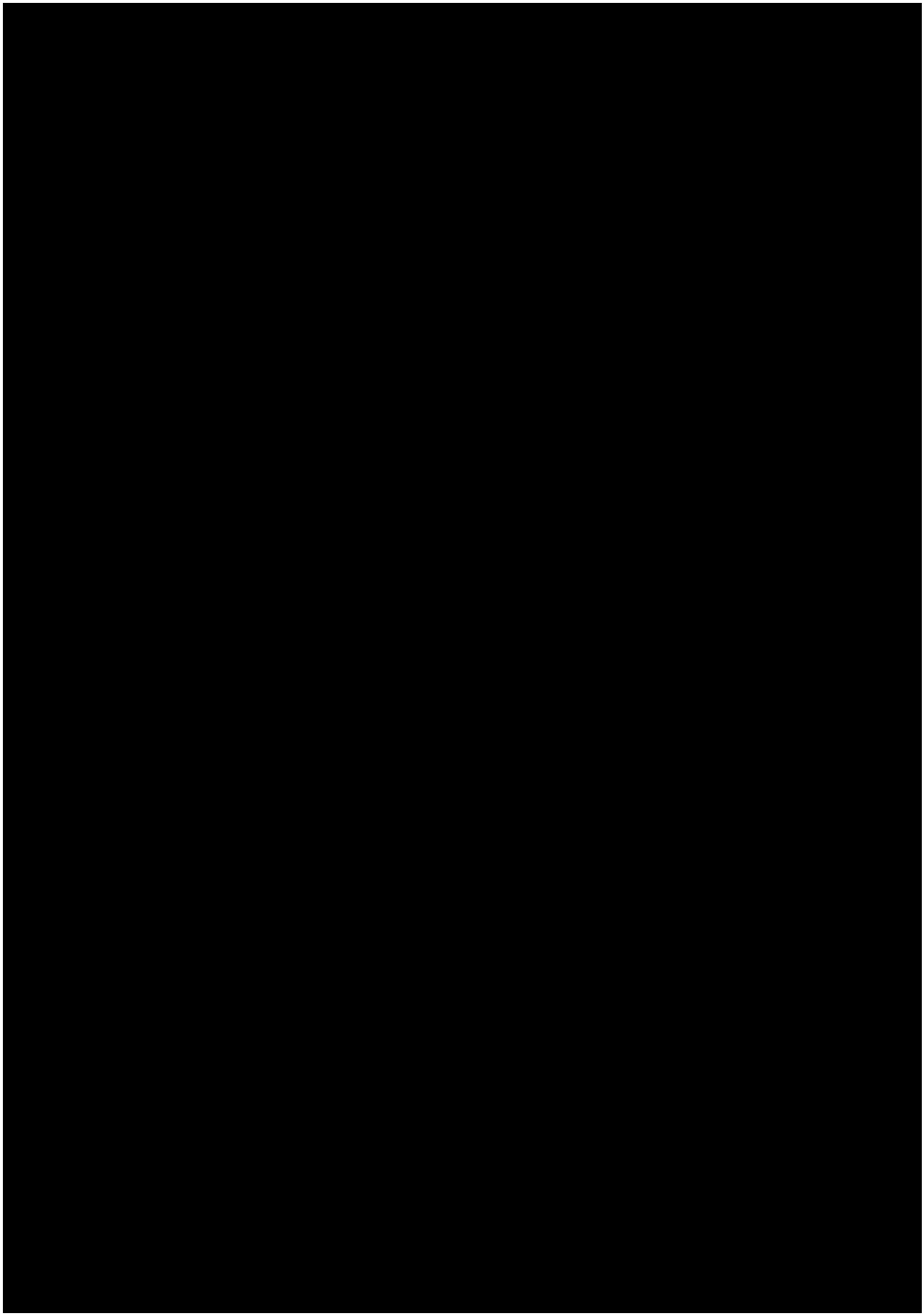


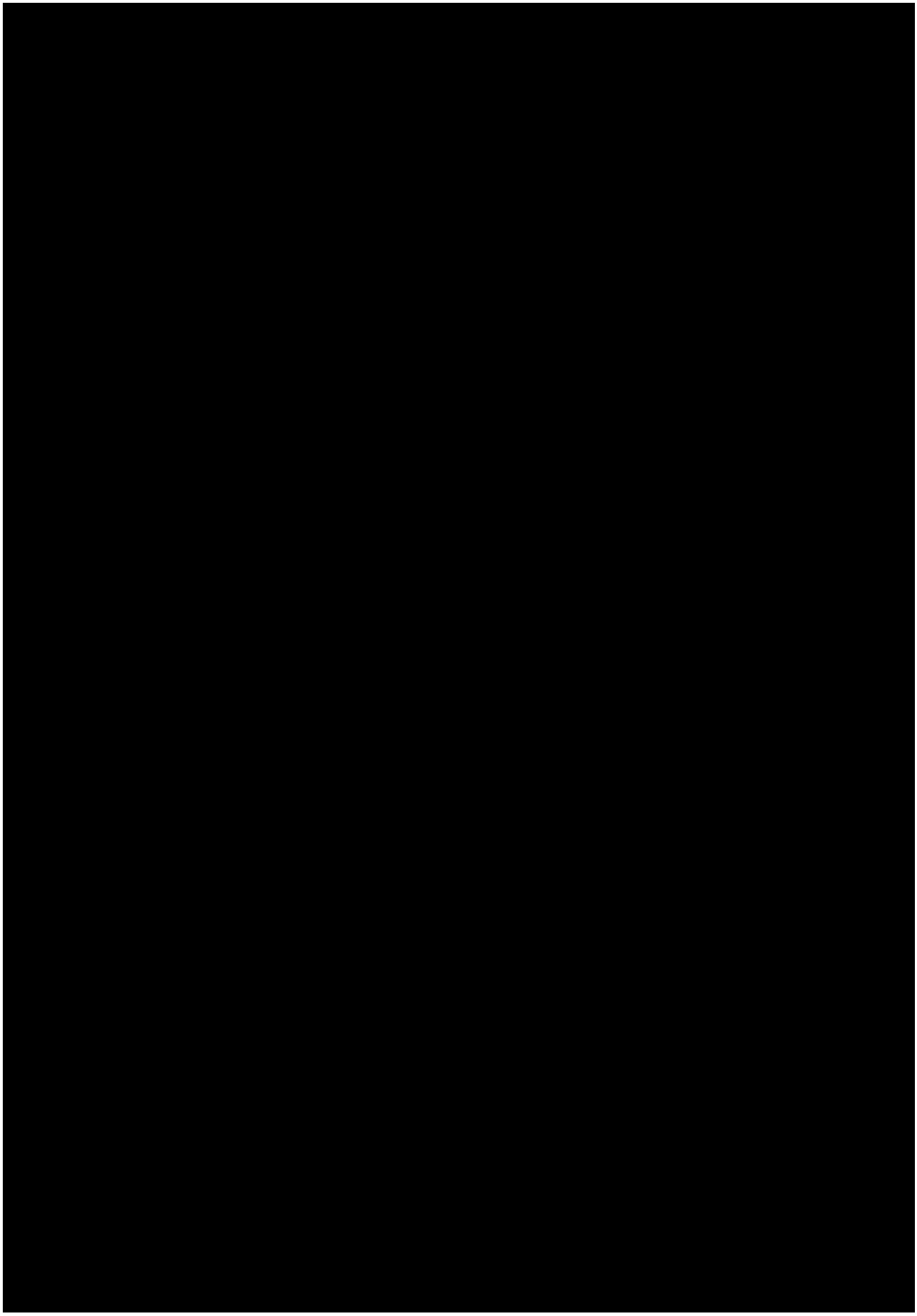


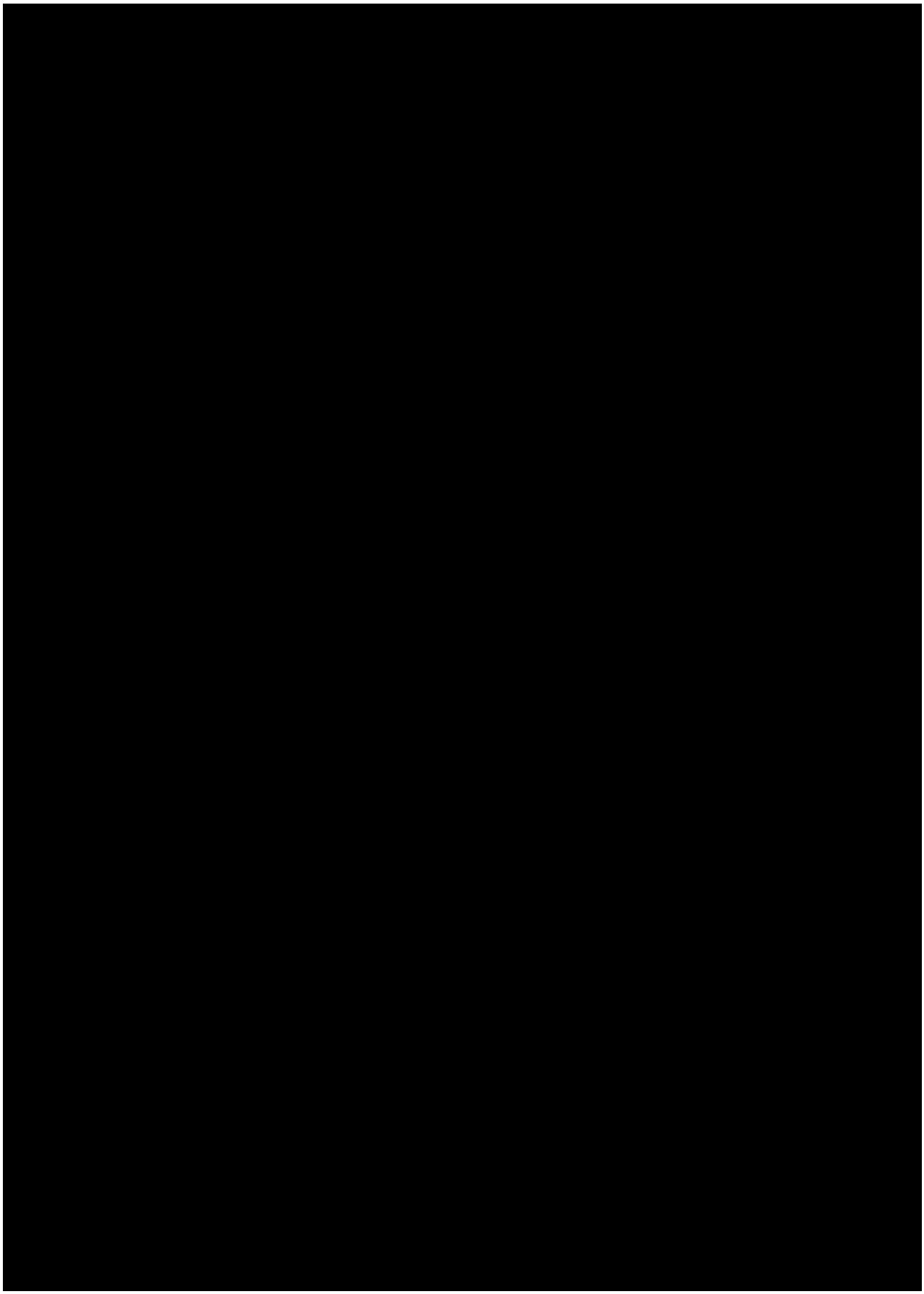




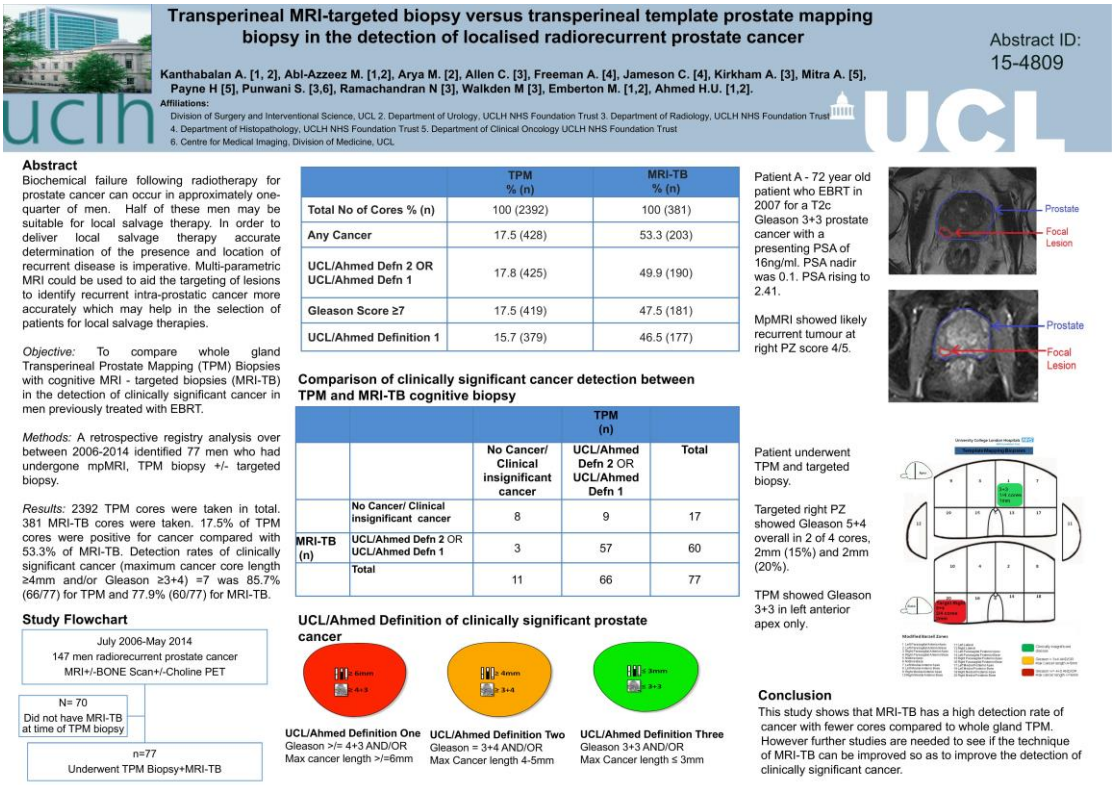








11.6 Presentation at European Association of Urology 2015 Targeted transperineal prostate biopsy versus transperineal prostate mapping biopsy in the detection of radiorecurrent prostate cancer



Transperineal MRI-targeted biopsy versus transperineal template prostate mapping biopsy in the detection of localised radiorecurrent prostate cancer

Abstract ID: 15-4809

Kanthabalan A. [1, 2], Abi-Azzeez M. [1,2], Arya M. [2], Allen C. [3], Freeman A. [4], Jameson C. [4], Kirkham A. [3], Mitra A. [5], Payne H [5], Punwani S. [3,6], Ramachandran N [3], Walkden M [3], Emberton M. [1,2], Ahmed H.U. [1,2].

Affiliations:
Division of Surgery and Interventional Science, UCL 2. Department of Urology, UCLH NHS Foundation Trust 3. Department of Radiology, UCLH NHS Foundation Trust
4. Department of Histopathology, UCLH NHS Foundation Trust 5. Department of Clinical Oncology UCLH NHS Foundation Trust
6. Centre for Medical Imaging, Division of Medicine, UCL

Abstract

Biochemical failure following radiotherapy for prostate cancer can occur in approximately one-quarter of men. Half of these men may be suitable for local salvage therapy. In order to deliver local salvage therapy accurate determination of the presence and location of recurrent disease is imperative. Multi-parametric MRI could be used to aid the targeting of lesions to identify recurrent intra-prostatic cancer more accurately which may help in the selection of patients for local salvage therapies.

Objective: To compare whole gland Transperineal Prostate Mapping (TPM) Biopsies with cognitive MRI - targeted biopsies (MRI-TB) in the detection of clinically significant cancer in men previously treated with EBRT.

Methods: A retrospective registry analysis over between 2006-2014 identified 77 men who had undergone mpMRI, TPM biopsy +/- targeted biopsy.

Results: 2392 TPM cores were taken in total. 381 MRI-TB cores were taken. 17.5% of TPM cores were positive for cancer compared with 53.3% of MRI-TB. Detection rates of clinically significant cancer (maximum cancer core length ≥4mm and/or Gleason ≥3+4) =7 was 85.7% (66/77) for TPM and 77.9% (60/77) for MRI-TB.

Study Flowchart

July 2006-May 2014
147 men radiorecurrent prostate cancer
MRI+/-BONE Scan+/-Choline PET

N= 70
Did not have MRI-TB at time of TPM biopsy

n=77
Underwent TPM Biopsy+MRI-TB

	TPM % (n)	MRI-TB % (n)
Total No of Cores % (n)	100 (2392)	100 (381)
Any Cancer	17.5 (428)	53.3 (203)
UCL/Ahmed Defn 2 OR UCL/Ahmed Defn 1	17.8 (425)	49.9 (190)
Gleason Score ≥7	17.5 (419)	47.5 (181)
UCL/Ahmed Definition 1	15.7 (379)	46.5 (177)

Comparison of clinically significant cancer detection between TPM and MRI-TB cognitive biopsy

		TPM (n)		
		No Cancer/ Clinical insignificant cancer	UCL/Ahmed Defn 2 OR UCL/Ahmed Defn 1	Total
MRI-TB (n)	No Cancer/ Clinical insignificant cancer	8	9	17
	UCL/Ahmed Defn 2 OR UCL/Ahmed Defn 1	3	57	60
	Total	11	66	77

UCL/Ahmed Definition of clinically significant prostate cancer

UCL/Ahmed Definition One
Gleason >/= 4+3 AND/OR
Max cancer length >/=6mm

UCL/Ahmed Definition Two
Gleason = 3+4 AND/OR
Max Cancer length 4-5mm

UCL/Ahmed Definition Three
Gleason 3+3 AND/OR
Max Cancer length ≤ 3mm

Patient A - 72 year old patient who EBRT in 2007 for a T2c Gleason 3+3 prostate cancer with a presenting PSA of 16ng/ml. PSA nadir was 0.1. PSA rising to 2.41.

MpMRI showed likely recurrent tumour at right PZ score 4/5.

Patient underwent TPM and targeted biopsy.

Targeted right PZ showed Gleason 5+4 overall in 2 of 4 cores, 2mm (15%) and 2mm (20%).

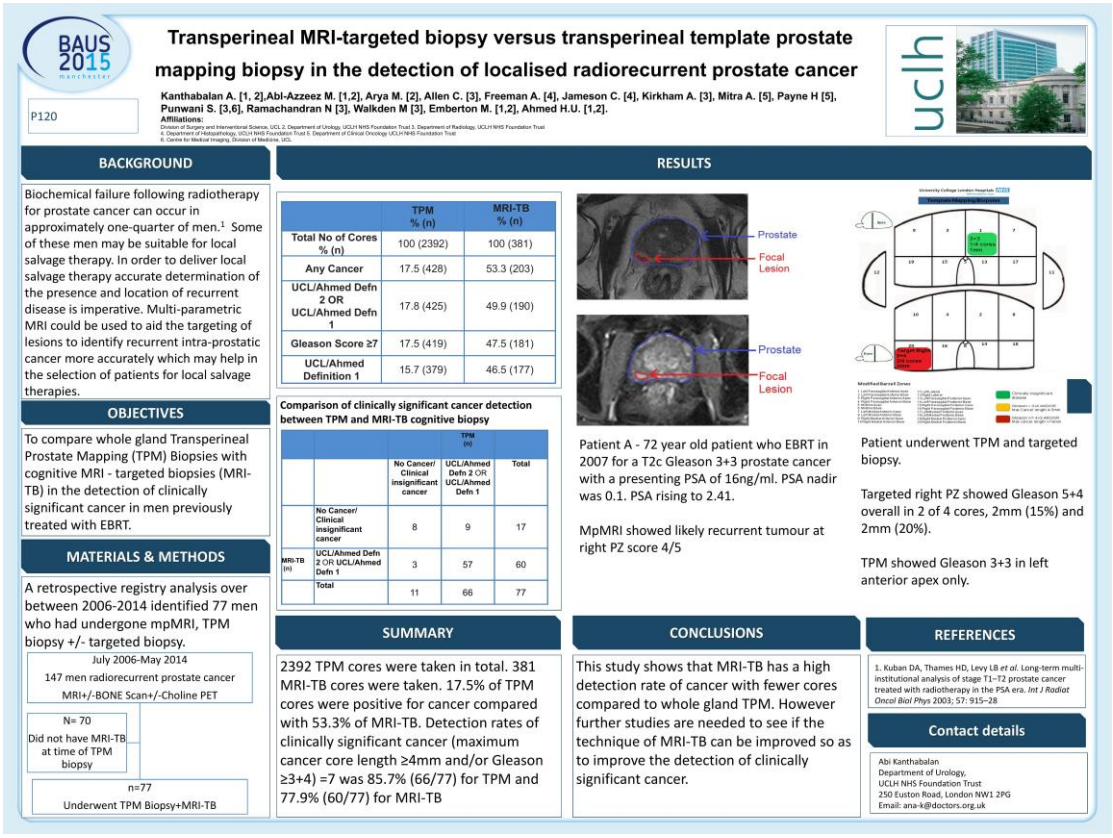
TPM showed Gleason 3+3 in left anterior apex only.

Conclusion

This study shows that MRI-TB has a high detection rate of cancer with fewer cores compared to whole gland TPM. However further studies are needed to see if the technique of MRI-TB can be improved so as to improve the detection of clinically significant cancer.

11.7 Presentation at British Association of Urological Surgeons 2015

Targeted transperineal prostate biopsy versus transperineal prostate mapping biopsy in the detection of radiorecurrent prostate cancer



Transperineal MRI-targeted biopsy versus transperineal template prostate mapping biopsy in the detection of localised radiorecurrent prostate cancer

BAUS 2015 manchester

P120

Kanthabalan A. [1, 2],Abl-Azzeez M. [1,2], Arya M. [2], Allen C. [3], Freeman A. [4], Jameson C. [4], Kirkham A. [3], Mitra A. [5], Payne H [5], Punwani S. [3,6], Ramachandran N [3], Walkden M [3], Emberton M. [1,2], Ahmed H.U. [1,2].

Affiliations:
Division of Surgery and Interventional Science, UCL 2. Department of Urology, UCLH NHS Foundation Trust 3. Department of Radiology, UCLH NHS Foundation Trust 4. Department of Histopathology, UCLH NHS Foundation Trust 5. Department of Clinical Oncology UCLH NHS Foundation Trust 6. Centre for Medical Imaging, Division of Medicine, UCL.

ucl h

BACKGROUND

Biochemical failure following radiotherapy for prostate cancer can occur in approximately one-quarter of men.[1] Some of these men may be suitable for local salvage therapy. In order to deliver local salvage therapy accurate determination of the presence and location of recurrent disease is imperative. Multi-parametric MRI could be used to aid the targeting of lesions to identify recurrent intra-prostatic cancer more accurately which may help in the selection of patients for local salvage therapies.

OBJECTIVES

To compare whole gland Transperineal Prostate Mapping (TPM) Biopsies with cognitive MRI - targeted biopsies (MRI-TB) in the detection of clinically significant cancer in men previously treated with EBRT.

MATERIALS & METHODS

A retrospective registry analysis over between 2006-2014 identified 77 men who had undergone mpMRI, TPM biopsy +/- targeted biopsy.

July 2006-May 2014
147 men radiorecurrent prostate cancer
MRI+/-BONE Scan+/-Choline PET

N= 70
Did not have MRI-TB at time of TPM biopsy

n=77
Underwent TPM Biopsy+MRI-TB

RESULTS

	TPM % (n)	MRI-TB % (n)
Total No of Cores % (n)	100 (2392)	100 (381)
Any Cancer	17.5 (428)	53.3 (203)
UCL/Ahmed Defn 2 OR UCL/Ahmed Defn 1	17.8 (425)	49.9 (190)
Gleason Score ≥7	17.5 (419)	47.5 (181)
UCL/Ahmed Definition 1	15.7 (379)	46.5 (177)

Comparison of clinically significant cancer detection between TPM and MRI-TB cognitive biopsy

		TPM (n)		
		No Cancer/ Clinical insignificant cancer	UCL/Ahmed Defn 2 OR UCL/Ahmed Defn 1	Total
MRI-TB (n)	No Cancer/ Clinical insignificant cancer	8	9	17
	UCL/Ahmed Defn 2 OR UCL/Ahmed Defn 1	3	57	60
	Total	11	66	77

Patient A - 72 year old patient who EBRT in 2007 for a T2c Gleason 3+3 prostate cancer with a presenting PSA of 16ng/ml. PSA nadir was 0.1. PSA rising to 2.41.

MpMRI showed likely recurrent tumour at right PZ score 4/5

Patient underwent TPM and targeted biopsy.

Targeted right PZ showed Gleason 5+4 overall in 2 of 4 cores, 2mm (15%) and 2mm (20%).

TPM showed Gleason 3+3 in left anterior apex only.

SUMMARY

2392 TPM cores were taken in total. 381 MRI-TB cores were taken. 17.5% of TPM cores were positive for cancer compared with 53.3% of MRI-TB. Detection rates of clinically significant cancer (maximum cancer core length ≥4mm and/or Gleason ≥3+4) =7 was 85.7% (66/77) for TPM and 77.9% (60/77) for MRI-TB

CONCLUSIONS

This study shows that MRI-TB has a high detection rate of cancer with fewer cores compared to whole gland TPM. However further studies are needed to see if the technique of MRI-TB can be improved so as to improve the detection of clinically significant cancer.

REFERENCES

1. Kuban DA, Thames HD, Levy LB *et al.* Long-term multi-institutional analysis of stage T1–T2 prostate cancer treated with radiotherapy in the PSA era. *Int J Radiat Oncol Biol Phys* 2003; 57: 915–28

Contact details

Abi Kanthabalan
Department of Urology,
UCLH NHS Foundation Trust
250 Euston Road, London NW1 2PG
Email: ana-k@doctors.org.uk